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The Pathophysiology of Combined Radiation Injuries
A Review and Analysis of the Literature on Non-Human Research

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One hundred and seventy one references applicable to determining the effect of tactical nuclear weapons on military personnel have been reviewed, and the significant conclusions are reported. The study reviews the scientific literature and focuses on animal experiments published from 1933 to the present time, including a number of German studies and some Soviet research not previously reviewed in English language publications. Recurring themes of the review are the synergistic increase in mortality when injury (burn, wound, bleeding, fracture, etc.) follows irradiation and the reduction in mortality when injury precedes irradiation and/or when antibiotics are administered.

The synergistic increases are attributed to radiation damage to the bone marrow precursor cells, which reduces the protective mechanisms (leukopenia) and permits easier onset of bacteremia and septicemia.

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Radiation in addition to favoring infection is also found to prolong and complicate the normal healing processes. The addition of burns or wounds shortens the latent period and results in earlier onset of the manifest illness phase.

SUMMARY

Thermal and Ionizing Radiation.

Synergistic increases in mortality have been demonstrated when animals were burned and irradiated, in particular, when the burn followed irradiation immediately to 20 days later. The synergism has been greatest when the irradiation is in the lethal range.

Alpen et al. found synergistic increases in mortality to 100 percent when rats were subjected to $LD_{20/30}$ 500-R X-irradiation and subsequent LD_{12} 26-pct burn. The synergistic increases were both in early shock and later infection and mortalities. Mild to moderate gut damage could have contributed to the shock condition (days 1-2) induced by the burn. A synergistic increase in mortality when sublethal burns follow LD_{10} irradiation was reported by Schildt.

Sublethal radiation (260 kV-pk X-rays) in combination with burn resulted at best only in an additive effect. However, an LD_{10} radiation dose given first followed by thermal injury up to 20 days postirradiation resulted in synergistic increases in mortality to nearly 100 pct. If sublethal burn preceded LD_{10} radiation, synergism was observed only if the burn preceded radiation by 5 days. Under the conditions of these experiments it appeared that thermal injury was a stronger trauma than sublethal X-irradiation, but an LD_{10} radiation preceding the burn caused a very strong synergistic effect.

Subsequent research indicates that the cause of increases in mortality during the first 3 days after combined trauma injuries is shock, probably resulting from blood loss into the burn. Beyond that time the open burn wounds and possible intestinal lesions become portals of entry for bacteria especially at the time when the irradiation injury has reduced or destroyed the immune barriers.

Attempts to demonstrate that early deaths in irradiated rats were due to gastrointestinal injury were not conclusively shown by the data presented by Baker and Valeriote. The conclusion reached by other authors that, at exposures up to 700 R, early deaths from combined injuries are caused by shock primarily due to the burn are more plausible.

One of the factors responsible for the increased mortality from the combination of radiation and burns is the effect of irradiation to reduce the numbers of leukocytes (leukopenia), facilitating onset of bacteremia and septicemia. Normally after burns and particularly with concomitant infection, one expects a leukocytosis. However, because of radiation damage to the bone marrow precursor cells, leukocytosis is not observed after combined injury of radiation and burns.

The microflora in animals subjected to combined injury is similar to that for burns alone, mainly streptococci, staphylococci and proteus. However, in combined injury, the number of positive cultures of bacteria is elevated in blood and the organs. This septicemia is the principle cause of the increased mortality.

Healing of burn wounds in irradiated animals is quite different from that in nonirradiated ones. This may be observed in all phases of the physiological repair. Time for healing is increased, the intensity of the reactive repair-regenerative process is reduced, there is a delay in discarding the burned, necrotic tissue, in epithelization, and in the formation of scar tissue. Complete healing of burns in sublethally irradiated animals may be delayed as many as 15-20 days. Often secondary or autoinfection (via injured intestine) complicate healing in burned and irradiated animals.

One may observe necrosis of granulations between days 21-25 in surviving rodents. During the subsequent manifest illness phase, breakdown of tissues of the burn wound and a general infection with strong intoxication of the animals is seen. During the delayed healing, bleeding of the center of the wound occurs mostly in the deep layer of the skin.

Experiments have shown that a 20-pct body burn in dogs resulted in 12 pct mortality, and exposure to 100 R X-rays was sublethal. When the dogs were subjected to both stresses simultaneously, a synergistic increase to 73 pct mortality was observed. Treatment with 900,000 units of penicillin reduced mortality to 14 pct.

A 10- to 15-pct burn in swine was sublethal, and a bilateral exposure to 400 R X-rays resulted in an LD_{20}. The combination of 400-R X-rays and a 10- to 15-pct burn synergistically increased mortality to 90 pct while treatment with streptomycin reduced it back to an LD_{20}.

Russian authors have reported that a result of combined burn and radiation injury is a shorter latent period and an earlier manifest period, shock, blood loss, and infection.

Blast and Ionizing Radiation

Blast from a nuclear detonation produces primary, secondary, and tertiary injuries. Primary or direct injuries are caused by blast wave overpressure acting on the body itself. The body organs primarily affected are those containing air or gas. Resulting injuries include lung hemorrhage, contusions or perforations of the gas-containing areas of the gastrointestinal tract, sinus hemorrhage, and ear drum rupture. The cause of death is often coronary embolism leading to cardiac arrest.

Very few studies have been conducted on primary blast injuries. Depending on the time postirradiation when sheep were subjected to air blasts, mortalities either increased synergistically or only additively. It was suggested that oscillations in the recovery of bone marrow precursors of blood cells were at least partly responsible for the periodic variations in the number of fatalities. In other experiments with sheep and swine, no increases in mortality were observed for the combined trauma.

Secondary or indirect injuries are caused by flying debris resulting in mechanical injuries (skin lacerations, tissue contusions, and penetrating wounds from flying missiles). Blood loss from deep wounds may induce hypovolemic shock. Animal experiments have shown that postirradiation hemorrhaging makes it difficult to treat injuries of irradiated patients. The predisposition to hemorrhage may last from 3-9 days until 45-50 days postirradiation depending on the size of the dose. The hemorrhagic condition not only affects the ability of animals and humans to survive but precludes even minor surgery.

In an experiment with mice, mortality was drastically reduced to 5 pct if they received a skin wound 8 days prior to an LD_{26} 500-R X-irradiation. A skin wound after radiation exposure on the same day increased mortality synergistically from 26 to 60 pct. This was increased further to 75 pct when wounding occurred two or eight days postirradiation.

In another experiment a skin wound immediately prior to 9 Gy ^{60}Co irradiation (LD_{94}) reduced mortality to 5 pct. However, the mortality of mice wounded immediately after irradiation was reduced only to 60 pct, and when wounded two days postirradiation, mortality increased to 100 pct.

Other factors that adversely affect the outcome of combined secondary blast and radiation injury are infection and radioactive contamination. Open wounds invite infection and radiation damages the immune response. Contamination with radioactive materials delays the healing process.

Tertiary blast injuries occur when the blast tumbles personnel in open terrain or impacts them against rigid surfaces. The effects may be skin wounds, fractures, and internal injuries. Experiments with the Noble-Collip drum reported by Schildt showed that sublethal radiation and LD_{10} drum trauma resulted at most in an additive effect whether radiation was first or second. The combination of LD_{10} radiation and sublethal drum trauma resulted in synergistic increases in mortality, greater when the radiation was first. This response was similar to that found with burn and radiation.

Experiments by McKenna and Zweifach showed that X-irradiation predisposed rats to traumatic shock when tumbled. The predisposition persisted for as long as 60 days for the higher radiation exposure levels. Hypotheses that the predisposition was due to infection or gastrointestinal injury were not confirmed by the experiments. Russian investigators concluded that irradiation affected the functional capability of the central nervous system, which would explain rapid drops in blood pressure soon after radiation exposure, which leads to increased sensitivity to subsequent traumas and eventually to shock.

The literature on the combination of fractures and irradiation showed that healing of fractures in irradiated animals was prolonged for both open and closed fractures. Experiments with rabbits showed that infection becomes a problem even with closed fractures due to radiation induced leukopenia. Open fractures of course have the same problems as open wounds. However, the overwhelming majority of animals that were irradiated, contaminated, and infected survived when antibiotics were used and the wound was closed within three days. An additional problem in such injuries is the possible incorporation of radioisotopes in the mending bone.

Other Combined Injuries

CBA male mice subjected concurrently to a sublethal scald burn and LD_{10} mechanical injury from the Noble-Collip rotating drum, either being first, suffered a 55 pct mortality. This increase was greater than that sustained (30% mortality) when another group of mice was concurrently subjected to the combination of a sublethal mechanical injury and an LD_{10} scald burn, either being first. Beyond day 0, synergistic increases in mortality are observed only when the animals are subjected to sublethal burn first followed by LD_{10} mechanical injury one to three days later or LD_{10} burn first and sublethal mechanical injury one day later. No synergistic injuries occurred beyond day 3. It appears then that the combination of burn and mechanical injuries resulted in synergistic increases in mortality only when shock has been induced by the trauma.

When rats were subjected to LD_{10} mixed neutron-gamma radiation, LD_5 blast, and sublethal burn on the same day, a synergistic increase in mortality to 64 pct resulted. The mortality decreased when the blast and burn were applied on later days.

Infection and Ionizing Radiation

The increased number of postirradiation mortalities in animals concurrently subjected to infectious agents have been ascribed to

1) increased permeability of skin surfaces and mucous membranes,
2) reduced numbers of granulocytes,
3) weakening of the phagocytic activity of the reticuloendothelial system, and
4) a reduced immuno-capability.

CBA mice subjected to bacterial toxin three days before irradiation exhibited a significantly lower mortality than expected. When they were subjected to the toxin on the same or later days, synergistic increases in mortality were observed. The decrease in mortality when toxin is administered before irradiation is attributed to an increase in hematopoesis in response to the toxin. When the toxin is administered after irradiation, very little defense can be mobilized, which results in the synergistic increases. These results are similar to those obtained with combined burn or mechanical injury and radiation and suggests that infection plays an important role between days 8 and 20 postirradiation.

In dogs, sixfold increases in leukocyte concentrations were noted for 14 days after gunshot wounds. However, leukocytosis was completely absent in dogs subjected to sublethal irradiation, and reached a nadir 20 days after irradiation. A further decrease in leukocytes was observed in animals that were subjected to the combined injuries of radiation and wounding. Recovery was not observed until 50 days after irradiation. This same response was noted in rabbits and guinea pigs.

Properdins are an important defense against infection. Their concentration in blood is greatly reduced within a few days to two weeks after hemorrhage or irradiation which deprives the animals of their natural protective ability.

Recent tests indicated that either GM-CSF or TDM in combination with antibiotics may further enhance survival after exposure to combined radiation injuries as long as pluripotential stem cells have survived.

In general, injuries sustained from combined radiation trauma are similar to those from radiation alone. However, combined radiation trauma usually reduces the latent period and manifest illness appears much sooner. Shock occurs more often, and the final disease is usually much more severe as indicated by synergistic increases in mortality.

PREFACE

As part of a contract with the Defense Nuclear Agency, Technico Southwest was asked to evaluate and model the effects of combined injuries from nuclear weapons on soldier performance and mortality. Technico Southwest is fortunate in obtaining the services of Dr. Siegmund Baum, who has actively researched and supervised research on the effects of ionizing radiation for 30 years, most recently as Chairman of the Experimental Hematology Department at the Armed Forces Radiobiology Research Institute in Bethesda and as Adjunct Professor of Physiology at the Uniformed Services University of the Health Science (USUHS).

The report that Dr. Baum has prepared is a comprehensive review and, most importantly, an analysis of the animal studies on combined radiation injuries. It covers 40 years of research and includes a number of German studies as well as some Soviet research not previously reviewed in English language reports or journals.

Because the report is intended to provide a basis for inferring the effects of combined injury on healthy, well-conditioned humans, its focus is on the mechanisms that affect survivability and on the postirradiation times of military interest. Included are graphs of data from the more pertinent articles that were reviewed.

CONVERSION TABLE

Conversion factors for U.S. Customary to metric (SI) units of measurement.

MULTIPLY ⟶ BY ⟶ TO GET
TO GET ⟵ BY ⟵ DIVIDE

angstrom	1.000 000 X E -10	meters (m)
atmosphere (normal)	1.013 25 X E +2	kilo pascal (kPa)
bar	1.000 000 X E +2	kilo pascal (kPa)
barn	1.000 000 X E -28	meter^2 (m^2)
British thermal unit (thermochemical)	1.054 350 X E +3	joule (J)
calorie (thermochemical)	4.184 000	joule (J)
cal (thermochemical)/cm^2	4.184 000 X E -2	mega joule/m^2 (MJ/m^2)
curie	3.700 000 X E +1	giga becquerel (GBq)*
degree (angle)	1.745 329 X E -2	radian (rad)
degree Fahrenheit	T_K=(t°f+459.67)/1.8	degree kelvin (K)
electron volt	1.602 19 X E -19	joule (J)
erg	1.000 000 X E -7	joule (J)
erg/second	1.000 000 X E -7	watt (W)
foot	3.048 000 X E -1	meter (m)
foot-pound-force	1.355 818	joule (J)
gallon (U.S. liquid)	3.785 412 X E -3	meter^3 (m^3)
inch	2.540 000 X E -2	meter (m)
jerk	1.000 000 X E +9	joule (J)
joule/kilogram (J/kg) (radiation dose absorbed)	1.000 000	Gray (Gy)**
kilotons	4.183	terajoules
kip (1000 lbf)	4.448 222 X E +3	newton (N)
kip/inch^2 (ksi)	6.894 757 X E +3	kilo pascal (kPa)
ktap	1.000 000 X E +2	newton-second/m^2 (N-s/m^2)
micron	1.000 000 X E -6	meter (m)
mil	2.540 000 X E -5	meter (m)
mile (international)	1.609 344 X E +3	meter (m)
ounce	2.834 952 X E -2	kilogram (kg)
pound-force (lbf avoirdupois)	4.448 222	newton (N)
pound-force inch	1.129 848 X E -1	newton-meter (N·m)
pound-force/inch	1.751 268 X E +2	newton/meter (N/m)
pound-force/foot^2	4.788 026 X E -2	kilo pascal (kPa)
pound-force/inch^2 (psi)	6.894 757	kilo pascal (kPa)
pound-mass (lbm avoirdupois)	4.535 924 X E -1	kilogram (kg)
pound-mass-foot^2 (moment of inertia)	4.214 011 X E -2	kilogram-meter^2 (kg·m^2)
pound-mass/foot^3	1.601 846 X E +1	kilogram/meter^3 (kg/m^3)
rad (radiation dose absorbed)	1.000 000 X E -2	Gray (Gy)**
roentgen	2.579 760 X E -4	coulomb/kilogram (C/kg)
shake	1.000 000 X E -8	second (s)
slug	1.459 390 X E +1	kilogram (kg)
torr (mm Hg, 0°C)	1.333 22 X E -1	kilo pascal (kPa)

* The becquerel (Bq) is the SI unit of radioactivity; 1 Bq = 1 event/s.
**The Gray (Gy) is the SI unit of absorbed radiation.

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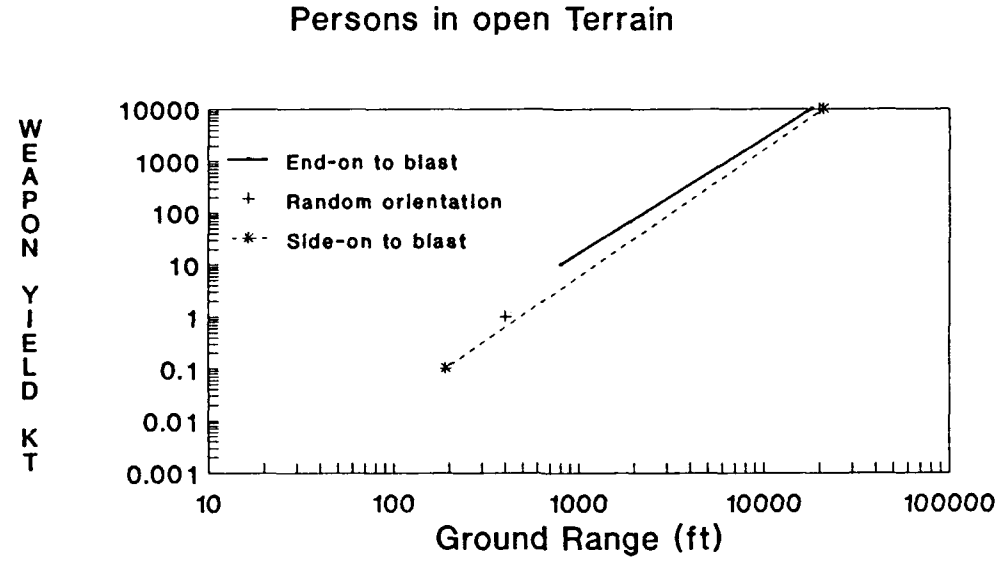
SECTION 1

INTRODUCTION

Casualties from the detonation of nuclear weapons may experience the combined effect of injuries due to ionizing radiation, thermal radiation, and blast (Ref. 108, 114). Exposure to thermal radiation results in burns that, depending on severity, can result in shock and/or subsequent infection. Exposure to ionizing radiation, depending on the dose, can damage the hematopoietic systems, which may severely diminish the ability of individuals to fight infection and survive. Bleeding into burn wounds may cause a severe fall in blood pressure, affect important brain centers, and result in shock. Blast produces a variety of injuries, which have been categorized as follows:

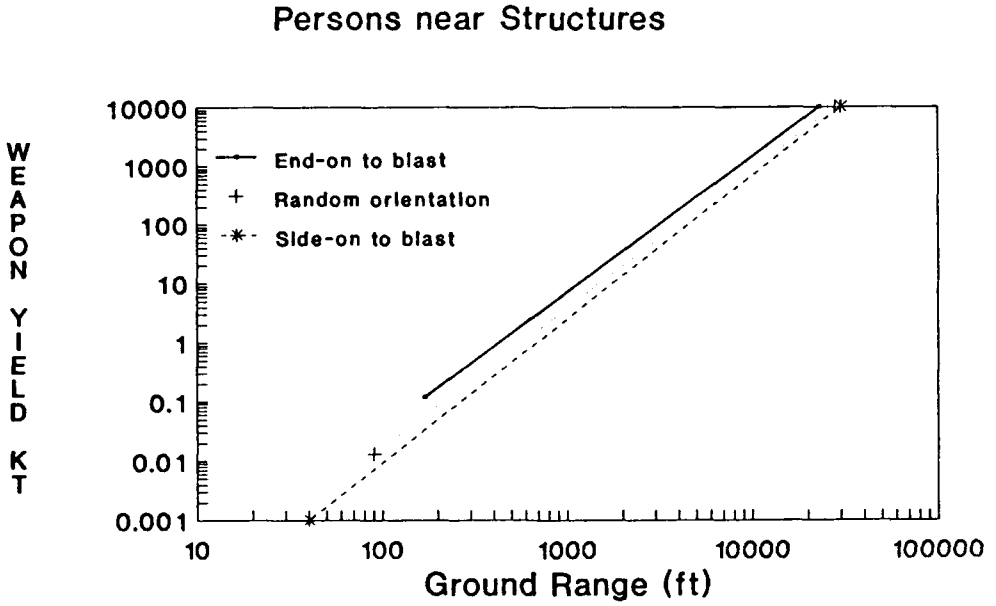
1. Primary or direct injuries are the effects of the blast wave overpressure, which injures the body itself (Ref. 164). The body organs primarily affected are those containing air or gas. Common injuries are lung hemorrhage, embolism, contusions or perforations of gas-containing portions of the gastroenteric tract, sinus hemorrhage, and eardrum rupture. The specific cause of deaths is usually coronary embolism; air bubbles occlude the coronary arteries and lead to cardiac arrest. This accounts for the short survival time of men and experimental animals subjected to primary blast effects. Liver and spleen ruptures are other common injuries caused by blast wave overpressure.

2. Secondary or indirect injuries are those caused by flying debris. These injuries are referred to as mechanical injuries and include skin lacerations, tissue contusions, and possibly penetrating wounds from flying missiles. Hypovolemic shock may result when a large amount of blood is lost from deep wounds in a short period of time.



Data from reference 166 (1979)

Figure 1. Range and weapon yield resulting in fifty percent probability of injuries to prone persons in open terrain from a surface burst.



Data from reference 166 (1979)

Figure 2. Range and weapon yield resulting in fifty percent probability of injuries to prone persons near structures from a surface burst.

3. Tertiary injuries are caused when blasts tumble bodies in open terrain or throw them against rigid surfaces. The resulting injuries include skin wounds, fractures, and damage to internal organs. The 50-pct probability of impact injuries to prone personnel in open terrain or near structures may be seen in figures 1 and 2 (Ref. 49, 166).

The high mortality and performance degradation seen in casualties at Hiroshima/Nagasaki was attributed to a synergistic interaction of one or more component injuries with effects of ionizing radiation (Refs. 26, 44, 45, 104); the number killed was much higher than would have been expected of individual burn and blast components or irradiation acting independently, and the evaluation of the combined effects of a nuclear detonation is important in planning civilian defense and military operations.

Other than the Hiroshima/Nagasaki events, the only data on combined injury in humans, where one of the components is ionizing radiation, are those obtained on victims of accidents during the conduct of nuclear research or in operation of nuclear power plants. A quantitative evaluation of the effect of the component combinations on healthy trained personnel is difficult to make from these sources because of uncertainties in the dose received and the scarcity of accident data. Consequently, most of our quantitative data on the effect of combined injury applicable to nuclear detonations comes from research with animals (Ref. 126), and its effect on humans must be inferred.

The types of injuries resulting from the detonation of a nuclear device include the combined effect of ionizing radiation and (1) thermal radiation effects (burns), (2) primary blast effects, 3) secondary blast effects, 4) tertiary blast effects, or 5) other combinations of these. Of primary interest are the mortality, pathophysiology, and healing processes associated with these injuries and the implications of their effect on personnel performance. Because only scant information is available on humans, the information and conclusions presented in this report are based on an intensive examination of the pertinent animal research literature.

SECTION 2

THERMAL AND IONIZING RADIATION

The effects of nearly simultaneous thermal and ionizing radiation were demonstrated in experiments by Alpen et al. (Ref. 5) and Sheline et al. (Ref. 133). Rats were exposed to 0, 100, 250, or 500 R of 250-kV-pk X-rays and were burned within one hour with water at 80°C temperature for 25 seconds. The percentage of the body area burned was increased from 0 to 37 pct. The results observed are summarized in figure 3A to 3D.

None of the animals exposed to 100 and 250 R of X-rays died unless they were also burned. Rats exposed to 500 R of X-rays alone had a 21-pct mortality over thirty days ($LD_{21/30}$) with all deaths occurring between days 4-30. The mortality of rats that received no irradiation and with burns covering less than 24 pct of total body surface area was 0; the mortality of such rats with a 24-pct burn was 11-pct; the mortality with a 37-pct burn increased to 100 pct (figure 3A). Nearly all deaths due to burn alone occurred early, within the first two days; the animals were in severe shock with lowered body temperature, shallow respiration, and hemoglobinuria. Of those surviving the first three days, a much smaller number (4 out of 50) died later, from days 4-30 (Ref. 5).

The early mortalities (days 1-2) due to burn alone were increased slightly to moderately if the rats were exposed to 100 R of X-rays (figure 3B) before being burned. The late mortalities (days 4-30) were only moderately increased by the irradiation.

The two traumas, 250 R exposure to X-rays followed by burn, contributed about equally toward mortality (figure 3C). Although early deaths were shifted towards lesser body burns, according to statistical tests by the authors, the distribution of tolerance to burn was unchanged by irradiation (Ref. 5). The exposure to 250 R of X-rays before the burn significantly increased the mortality over that obtained with burn alone (figure 3C).

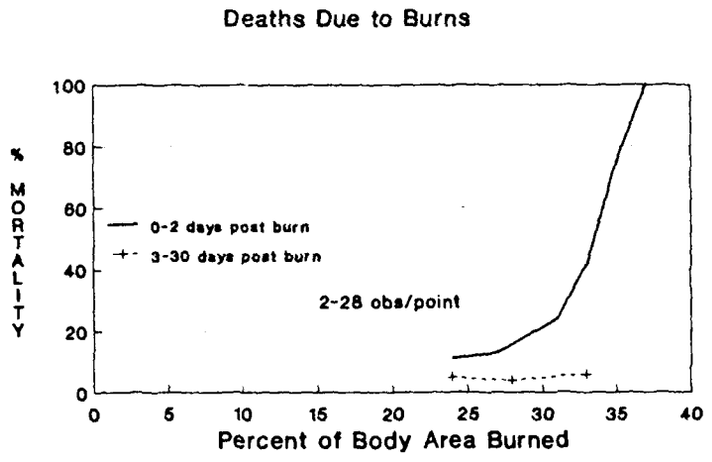


Figure 3A

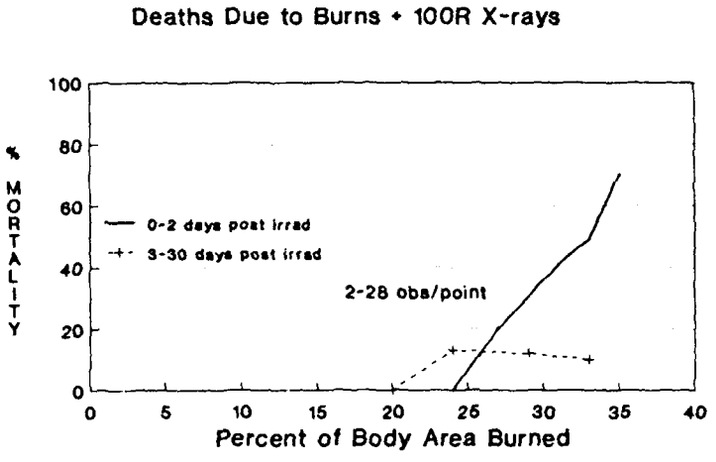


Figure 3B

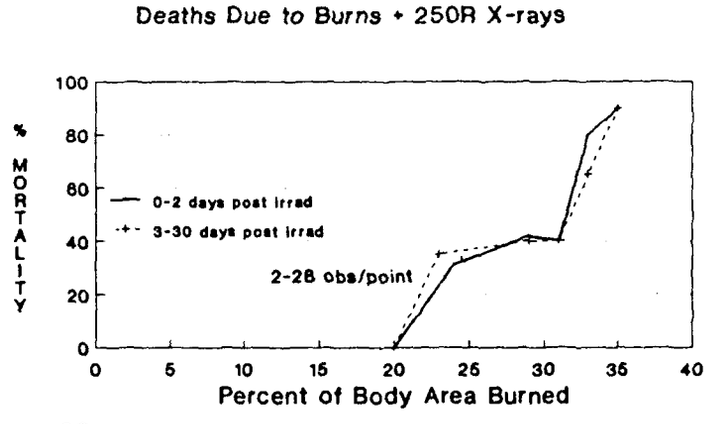


Figure 3C
Data for figures 3A-3d from reference 5 (1954)

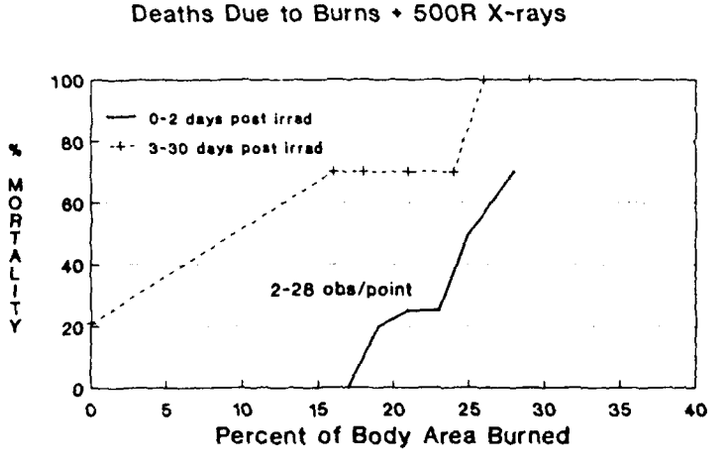
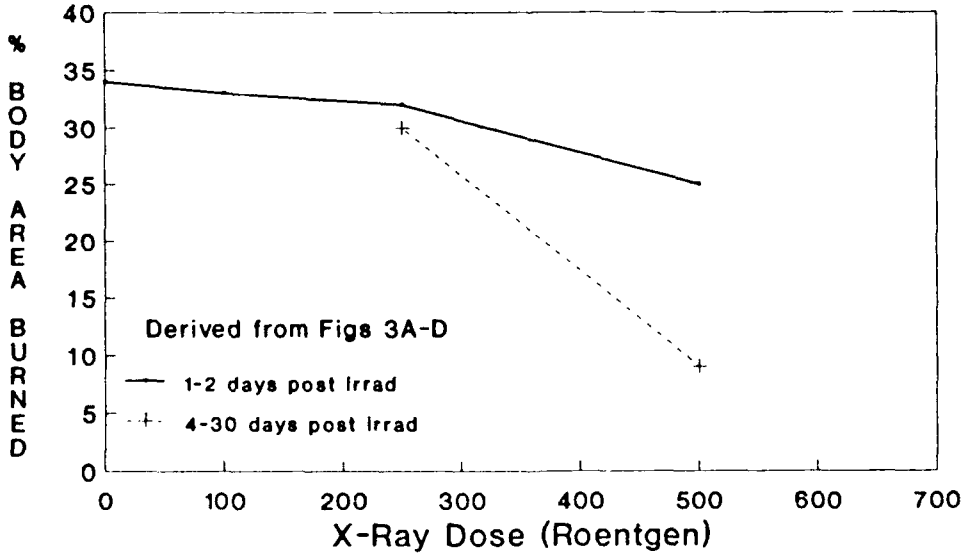


Figure 3D

Figure 3. Mortality as a function of combined burn area and total body x-ray exposure.

The addition of 500 R of X-rays to burn injuries (Ref. 5) clearly showed that this radiation exposure is a much more lethal component than the burns (figure 3D). This is supported by the data in figure 4, which shows that a 9-pct burn in combination with 500-R exposure of X-rays causes an $LD_{50/30}$ as compared with an $LD_{21/30}$ for radiation only and no deaths with burn only. There appeared to be a moderate synergistic increase in the early mortality (day 1-2). Moderate gastrointestinal injury, resulting from the same radiation exposure (Ref. 37), could have accentuated the burn shock in animals by contributing toward abnormal fluid distribution. An exposure of 500 R X-rays without burns caused a 21-pct mortality (figure 3D), and the addition of a 16-pct burn increased mortality synergistically to 71 pct. The addition of a 26-pct burn increased mortality to 100 pct, although a 26-pct burn alone resulted in only a 12-pct mortality, LD_{12} (figure 3A). Radiation appears to dominate in this combination of injuries, since the pattern of death between days 4-30 in the animals receiving the combined injury was similar to that seen in animals dying from X-irradiation alone.



Data from reference 5 (1954)

Figure 4. Burn area and X-ray exposure yielding 50% mortality in rats.

Bond et al. (Ref. 20) postulated that combined injury may unmask or accentuate lesions that would not be lethal if present in animals receiving either trauma alone. These authors observed a synergistic increase in mortality in the case of a pulmonary infection and X-irradiation. In this vein, Alpen et al. (Ref. 5) felt that although 100 R did not induce sufficiently severe lesions to increase mortality, the higher exposure of 250 R may have caused sufficient lesions to produce a synergistic increase in mortality from days 4 to 30. They also postulated that the animals' protective mechanisms against infection were so depressed by irradiation that they were are unable to cope with the infectious processes arising as a result of burn.

The pathophysiological explanation for the synergism may well be that the radiation damage to the bone marrow stem cells and precursor cells results in a decreased number of lymphocytes, macrophages, and granulocytes, which in turn degrades the antimicrobial defenses of the injured host (Ref. 75). The burn area provides an entry for bacteria into the immune-compromised host, and deaths due to septicemia follow.

Table 1. Effect of combined burn and radiation on dog mortality. (From Ref. 26)

	MORTALITY		Survival Time	Healing Time
	(Numbers)	(Percent)	(Days)	(Days)
A. 20% Body burn only	5/40	12	5-14	40
B. 100-R X-rays* alone	0/10	0	--	--
C. 20% Body Burn & 25-R X-rays	5/25	20	5-14	40
D. 20% Body Burn & 100-R X-rays	29/40	73	8-14	40
E. 20% Body burn, 100-R X-rays & Treatment**	4/28	14	8-14	28-42

*1-MeV pk; 17 R/min.
**900,000 units penicillin

Research by Brooks et al. (Ref. 26) with dogs and Baxter et al. (Ref. 13) with swine confirmed in large animals the findings of other investigators in rodents (Refs. 5, 8, 159). Brooks et al. subjected dogs to a standard, deep, second degree burn involving 20 pct of the skin surface area. Five of 40 dogs died resulting in a 12-pct mortality rate (Table 1). The addition of 100-R 1-MeV X-ray total body exposure to the 20-pct burn resulted in a sharp increase in mortality to 73 pct. The addition of only 25 R of X-rays increased the mortality of 12 pct for burn alone to 20 pct for the combination. Bacteriologic investigation indicated that a bacteremia developed in the burned dogs and in the dogs subjected to the combination. In the dogs that received a 20-pct burn only, the bacteremia was a transient phenomenon involving streptococci of low virulence. In the animals with combined injury, entrance in the blood of unhemolytic streptococci was shortly followed by invasion with more virulent beta hemolytic streptococci (dog types G & L) which induced a fatal septicemia in 73 pct of the animals. The authors suggested that radiation depresses the phagocytic activity and other defense mechanisms to a point where they are unable to localize the beta hemolytic streptococci at the wound surface.

The beneficial influence of penicillin therapy in sharply reducing the mortality of the dogs with combined injury indicated that this therapy might be helpful to humans exposed similarly. However, it would appear that usefulness of this type of therapy would be limited to radiation doses that primarily injure the bone marrow hematopoietic cells (Ref. 26).

Baxter et al. (Ref. 13) subjected 20 young Yorkshire hogs to 400-R total body X-rays (bilateral exposure, 10 R/minute) using a 220-kV-pk Roentgen ray therapy machine followed by a 10- to 15-pct thermal flash burn using 2.5 grams of magnesium powder and 17.5 grams of barium peroxide (maximum temperature of 2500^{o}C). Of these, 10 animals received 500 mg of streptomycin intramuscularly daily beginning 24 hours after trauma and continued for 21 days. As may be seen from Table 2, none of 10 hogs with a 10- to 15-pct thermal burn alone died. Bilateral exposure to 400-R X-rays induced two fatalities or 20 pct. The exposure of the swine to the combined injury of both traumas (radiation plus thermal burn) increased mor-

tality synergistically to 90 pct. Interestingly, the administration of streptomycin parenterally commencing 24 hours after exposure and continuing through 21 days post-trauma reduced the mortality to 20 pct (Table 2). Early and adequate treatment with streptomycin contributed to a reduction of mortality in swine following a total body radiation exposure that primarily injures the bone marrow hematopoietic stem cell and precursor system. In the unirradiated animal, the bone marrow contains the cells that provide protection against infection from the burns.

Table 2. Effect of combined burn, radiation and streptomycin on swine mortality. (From Ref. 13).

Insult and Treatment	Mortality at Day 0-5	6-30	>30
10-15% Area Burn	0/10	0/10	0/10
400R X-ray	0/10	2/10	0/10
X-Ray & Burn	0/10	9/10	0/10
X-Ray & Burn & Streptomycin (500 mg/day)	0/10	2/10	0/10

Alpen et al. (Ref. 5) suggested a possible contribution of radiation-induced gut injury for day-3 lethalities, particularly, at exposures of 500 R or more. A study by Valeriote and Baker (Ref. 159) using X-ray exposures of 550, 650, 700 and 750 R combined with a sublethal 16-pct burn in rats was designed to verify that suggestion. However, the authors assumed that all deaths to eight days postirradiation were caused by injury to the gastrointestinal (G.I.) system, and those beyond that time were caused by bone marrow damage. In discussing the gastrointestinal syndrome, Bond (Ref. 22) indicated that it is characterized by a relatively short survival time. This survival time is remarkably constant for families within species, but does vary from specie to specie. Therefore, in characterizing the LD_{50} for the G.I. syndrome, it is necessary to include cases that die a relatively short time after radiation. One must try to choose a time that is long enough to include essentially all deaths caused by the G.I. syndrome, but short enough to exclude any appreciable number of "early bone marrow deaths."

250 KvP X-ray alone

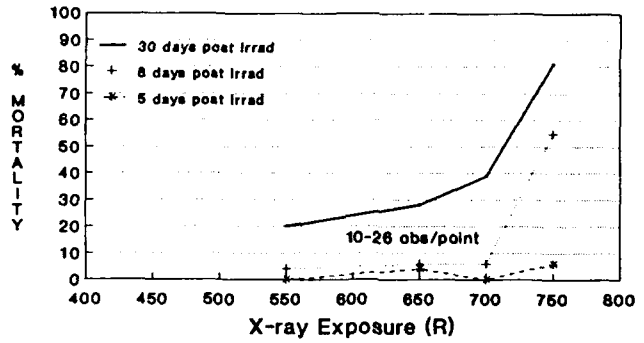


Figure 5A

250 KvP X-ray + 1 min. 16% Burn

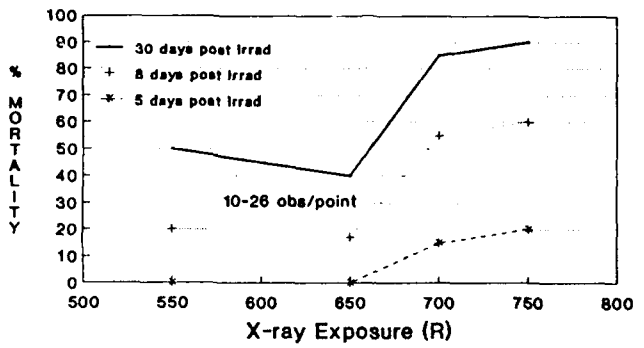


Figure 5B

250 Kvp X-ray + 1.5 min. 16% burn

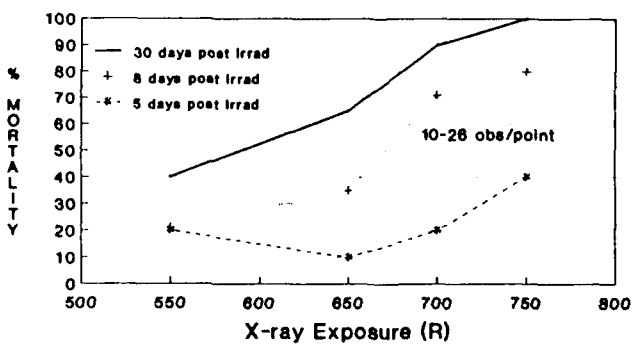


Figure 5C

Data for Figs 5A-5C from ref 159 (1964)

Figure 5. Combined effects of thermal burns and X-irradiation on early mortality in rats.

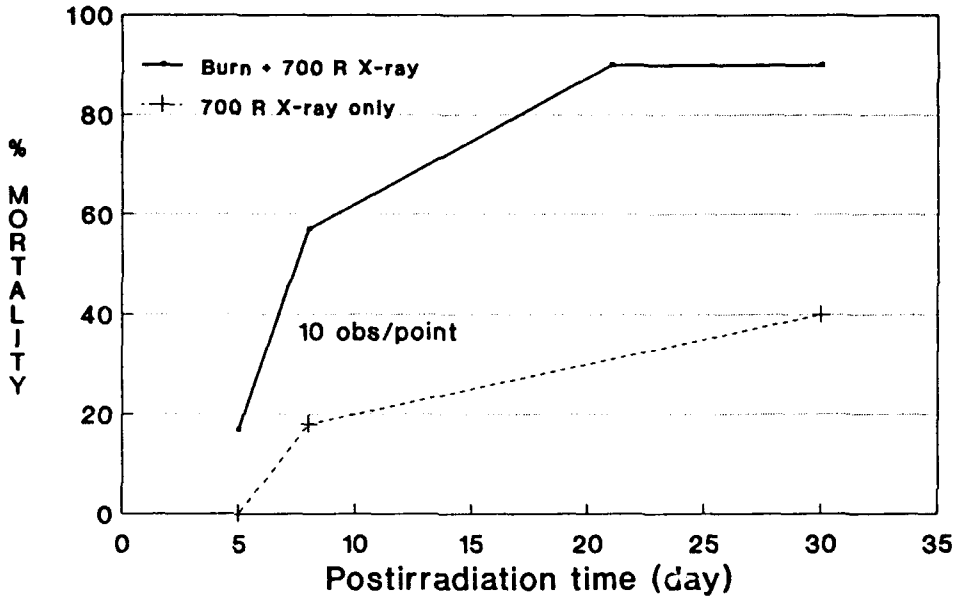
For species such as the mouse and the rat, which die characteristically at days 3-1/2 to 4 from the G.I. syndrome, an $LD_{50/5}$ is designated (Ref. 22). Monkeys and probably humans die by day 7, and the arbitrary cut off point is taken as 8 days for an $LD_{50/8}$.

Although Valeriote and Baker extended the cutoff point for rat G.I. mortality from 5 to 8 days postirradiation (Ref. 159), they found no G.I. effects for irradiation alone to exposures of 700 R (figure 5A). Only at an exposure of 750 R was a significant increase in mortality to day 8 observed. Examination of their data (figure 5A) for the number of deaths to day 5 shows that no significant increase in mortality had occurred up to an exposure of 750 R X-rays. Consequently, a major contribution by the G.I. syndrome up to exposures of 750 R is questionable.

Valeriote and Baker gave rats a 16-pct burn using a one-minute exposure to a 500-W infrared lamp and followed this 10 minutes later with X-ray exposures of 550 to 750 R. A moderate increase in 5-day mortalities occurred for the 700- to 750-R exposure (figure 5B). However, again it appears that the greater number of deaths was due to radiation-induced bone marrow failure. Between days 5 and 8, a significant decrease in white cell production due to the irradiation injury of the bone marrow stem and precursor cells is seen. Consequently, the defense against bacteria invading the burn wound is compromised, and death may be due to subsequent septicemia. It is possible that bacteria entering tissues from the injured intestine aggravate the pathophysiological condition caused by X-ray exposures of 700 R or greater; however, the authors' contention that the sublethal burn trauma in combination with X-irradiation increased mortality "in the time period characteristic of gastrointestinal injury" was not demonstrated by their own data (Ref. 159). Their further suggestion that the thermal trauma acted in a synergistic manner with the effect of X-irradiation on the gut is also questionable.

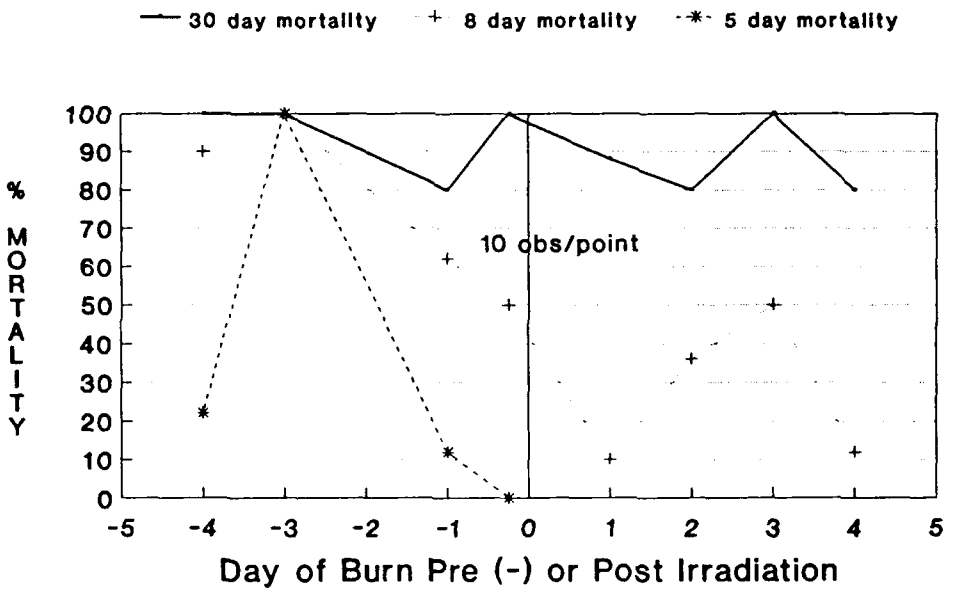
In a subsequent paper (Ref. 8), Baker and Valeriote showed (figure 6) that an exposure of 700 R X-rays caused no deaths in rats to 5 days after irradiation, an increase in mortality to 18 pct by day 8, and to 40 pct by day 30. A 16-pct burn inflicted at the same time as 700 R X-rays resulted in a 17-pct mortality by day 5, 57 pct by day 8, and 90 pct by day 21. Baker and Valeriote attributed the mortality to day 8 after irradiation to an inhibitory effect of toxic materials, produced at the site of the burn, on recovery of the intestinal epithelium from radiation damage; i.e., recovery from gut damage. Examination of the day 5 mortality data (figures 5A and 5B) shows none or a much smaller contribution of what might be true gut injury. A moderate effect of gut injury may be ascribed to the combination of a 16-pct burn and an exposure of 700 R X-rays, however, it is most likely that most of the deaths are caused by injury to the bone marrow. If we accept day 5 after irradiation as the cut off point for deaths in rats due to G.I. injury, then nearly all deaths must be attributed to injury to the bone marrow, because they occurred beyond day 5.

In other experiments performed by Baker and Valeriote (Ref. 8), 16-pct burns were administered to groups of rats daily from 4 days prior to an X-irradiation exposure of 700 R to 4 days after irradiation (figure 7). The resulting day 5 mortality data indicate none to small contributions to mortality by the burn except when the 16-pct burn was inflicted on day 3 prior to irradiation. In that group all rats died within 5 days of being irradiated (figure 7), and the authors offered no explanation. No groups burned after being irradiated had day-5 postirradiation deaths. One must conclude therefore, that G.I. injury did not play a role in the increase in mortality ascribed to the combination of a sublethal burn and X-irradiation exposures below 750 R. A more likely contributor to the increase is the condition of shock which may be observed after burn alone or after burn and X-irradiation for the first three days post-trauma (Ref. 5).



Data from reference 8 (1966)

Figure 6. The effect of concurrent thermal burn and X-irradiation on survival time of rats.



Data from reference 8 (1966)

Figure 7. The 5, 8 and 30 day mortality for various sequential combinations of burn and irradiation.

Schildt (Ref. 127) performed experiments to determine the effect of combined thermal injury (scald burn) and irradiation. Standardized burns that were sublethal, LD_S, or LD_{10}, were given in accordance with methods described in prior publications (Refs. 128, 129). The following symbols were used for the various traumas:

B_S = Sublethal burn

B_{10} = Burn that causes 10 pct lethality

R_S = Sublethal irradiation

R_{10} = Irradiation that causes 10 pct lethality

The symbol of the trauma that appears first was administered first.

Schildt (Ref. 127) reported that sublethal irradiation followed on the same day by an LD_{10} burn (R_S+B_{10}) resulted in a mortality of only 20 pct (figure 8A). Clearly, a sublethal radiation exposure with only moderate injury to the bone marrow does not contribute synergistically to mortality.

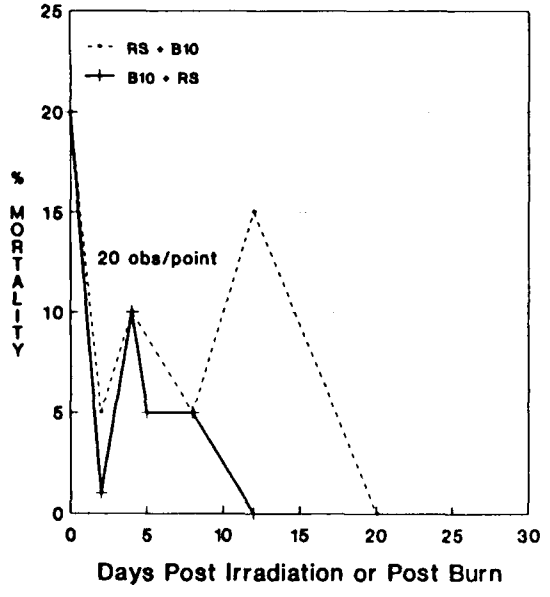


Figure 8A

Data from reference 127 (1972)

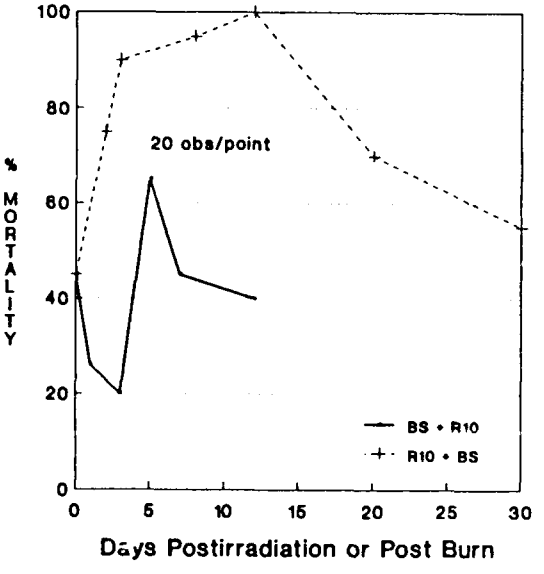


Figure 8B

Data from reference 127.

Figure 8. Mortality of mice for various sequential combinations of sublethal and LD_{10} burn and irradiation.

On the other hand, Schildt also reported that an LD_{10} X-irradiation (R_{10}) exposure, particularly if it is given to the animals first, is strongly synergistic when combined with sublethal burns (figure 8B). When the animals are subjected to R_{10} first and subsequently to a sublethal burn (B_S) between days 2 and 12 , the combination increases mortality synergistically to between 75 to 100 pct. When the rats are stressed with B_S first (figure 8B) and subsequently with R_{10} five days later, a synergistic increase to between 55 and 65 pct is observed. The higher increase between days 2 and 12 when R_{10} is given first probably is the result of greatly reduced numbers of granulocytes and macrophages caused by earlier radiation-induced bone marrow cellular damage. This compromises the defense against invading bacteria from the burns or other injuries.

The combination of burn and radiation results in a shortened latent period (the period absent of overt symptoms) and an earlier beginning of the manifest illness period (the period of obvious acute symptoms); experimental animals experience shock, blood loss, infection and lowering recovery potentials. Sillevaerts (Ref. 136) reports that the combination of burns and irradiation, even if the burns are not extensive, usually is severe and needs individual attention. Mice that were subjected only to burns lived almost three times as long as those with combined injury of burn and radiation (700 R X-rays). Mice with acute radiation disease became extremely sensitive to burn trauma (Ref. 39). Korcanov observed that small burns in addition to acute radiation exposure elevated lethality (Ref. 67).

A number of factors are responsible for the increased mortality from combined injury of burns and radiation (Ref. 33). One of these is the reduction of the protective mechanisms (leukopenia), which more easily permits bacteremia and septicemia. Normally after burns and particularly with concomitant infection, one expects a leukocytosis. However, due to radiation damage to the bone marrow precursor cells, no leukocytosis is observed after combined injury of radiation and burns (Refs. 28, 29, 141).

The microflora in animals subjected to combined injury is similar to that for burns alone, mainly streptococci, staphylococci, and proteus. However, in combined injury, the number of positive cultures of bacteria is elevated in blood and the organs. This septicemia explains the severity of the clinical picture and the increased lethality (Ref. 141). Healing of burn wounds in irradiated animals in all phases of the physiological repair mechanism is quite different from that in nonirradiated ones (Ref. 28). Time for healing is increased, the intensity of the reactive repair-regenerative process is reduced, there is a delay in discarding the burned necrotic tissue, in epithelization, and the formation of scar tissue. Complete healing of burns in sublethally irradiated animals may be delayed as many as 15-20 days (Ref. 33). Often secondary or autoinfection (via injured intestine) complicate healing in burned and irradiated animals.

Necrosis of granulations is observed on days 21-25 in surviving rodents (Ref. 167). During the subsequent manifest illness phase, breakdown of tissues of the burn wound and a general infection with strong intoxication of the animals is seen. During the delayed healing, bleeding of the center of the wound may be observed, mostly in the deep layer of the skin (Ref. 170).

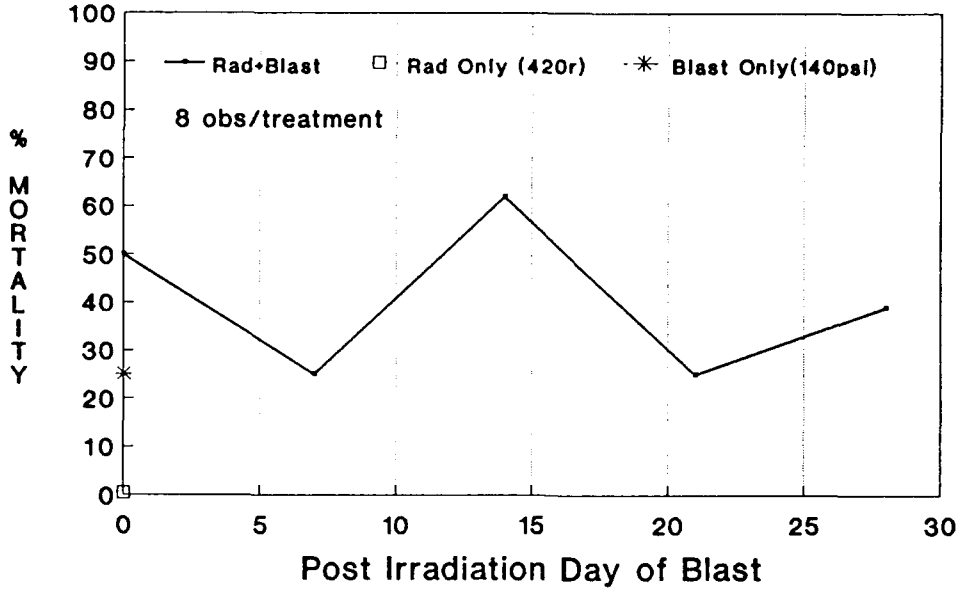
SECTION 3

BLAST AND IONIZING RADIATION

3.1 PRIMARY BLAST EFFECTS AND IONIZING RADIATION

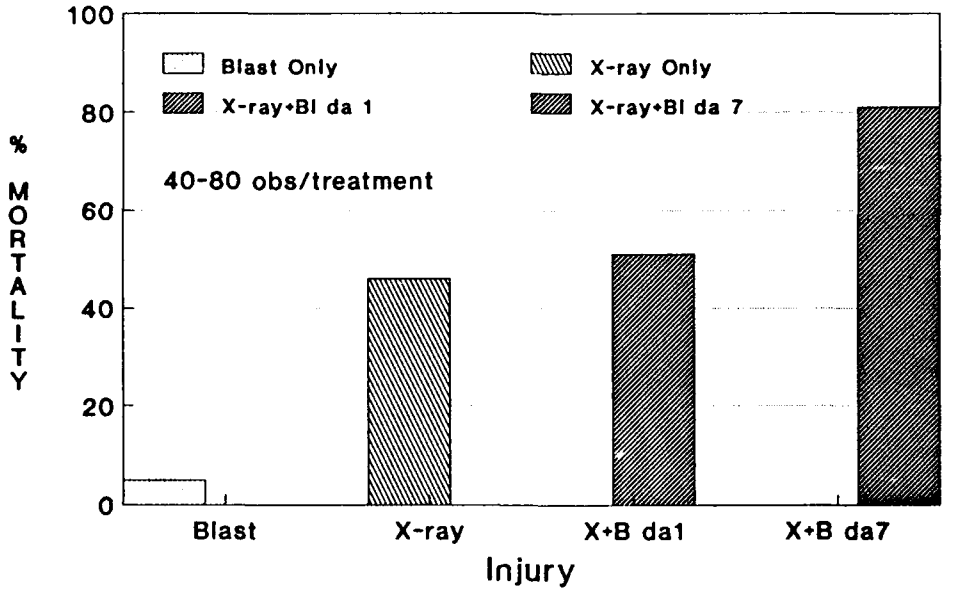
There have been few studies in which radiation was combined with airblast. Jones et al. (Ref. 64) exposed sheep bilaterally to an $LD_{20/60}$ dose of neutron-gamma radiation (410 to 445 rad) in combination with an LD_5 blast from 64-lb. high explosive charges with 3-ms pulse durations (figure 9). When both stresses were imposed on the same day, a synergistic increase in mortality to 50 pct was recorded, although an increase to only 25 pct should have been observed if the effects of radiation and blast were additive. Such an additive effect of 25 pct was observed when the sheep were subjected to the airblast 7 days after irradiation. However, when the animals were blasted 14 days after irradiation, a synergistic effect was again observed resulting in a 62-pct mortality. Mortality with blasting on day 21 after irradiation returned to 25 pct, and with blasting on day 28, a smaller increase to 38 pct was noted (figure 9).

The authors gave no explanation for the oscillatory responses (Ref. 64). However, postirradiation oscillatory or periodic recovery of the hematopoietic system has also been observed in rats and dogs (Refs. 10-12, 93, 94). In the dog, strong oscillations in hematopoietic recovery have been observed for 14 days after irradiation followed by milder ones up to 30 days (Ref. 12). Stressful perturbations of the bone marrow as caused by ionizing radiation may initiate a pulse stimulus acting on a basic oscillatory system (Ref 94). It is possible that the injuries caused by blasts are better protected from lethal infection when the hematopoietic system is in the recovery mode rather than during a period when blood cell production is decreasing. If the animals are subjected to airblasts that are capable of producing internal as well as external injuries at a postirradiation time when blood cell production is decreasing or at its lowest, then the defense against invading bacteria would be compromised, resulting in greater numbers of deaths (Ref. 64).



Data from reference 64 (1968)

Figure 9. Effect of nuclear radiation ($LD_{20/60}$) and blast (LD_5) on sheep.



Data from reference 115 (1968)

Figure 10. Effect of blast (LD_5) and radiation (LD_{46}) alone and in combination on rat mortality.

On the other hand, an increase in the number of leukocytes on day 7 and 21 would result in decreased mortality due to blast injuries and subsequent infection (Ref. 12). It is of interest to note that Sprague-Dawley rats subjected to an $LD_{46/30}$ 250-kV-pk X-ray exposure and to an LD_5 blast seven days later showed a synergistic increase in mortality to 81 pct (Ref. 115 and figure 10). It is quite possible therefore that the data obtained from sheep might not necessarily hold for other mammalian species.

In another experiment (Ref. 166), sheep were exposed to airblast (LD_{15}) and ^{60}Co gamma radiation ($LD_{25/60}$). When the animals were exposed to both stresses on the same day only 15 pct died, although 36 pct was expected. Furthermore, the animals died at a time indicating death due to irradiation and not blast. Because of the variability in responses, it is possible that the sample sizes (16-20 per group) for this experiment were not large enough to have drawn meaningful conclusions.

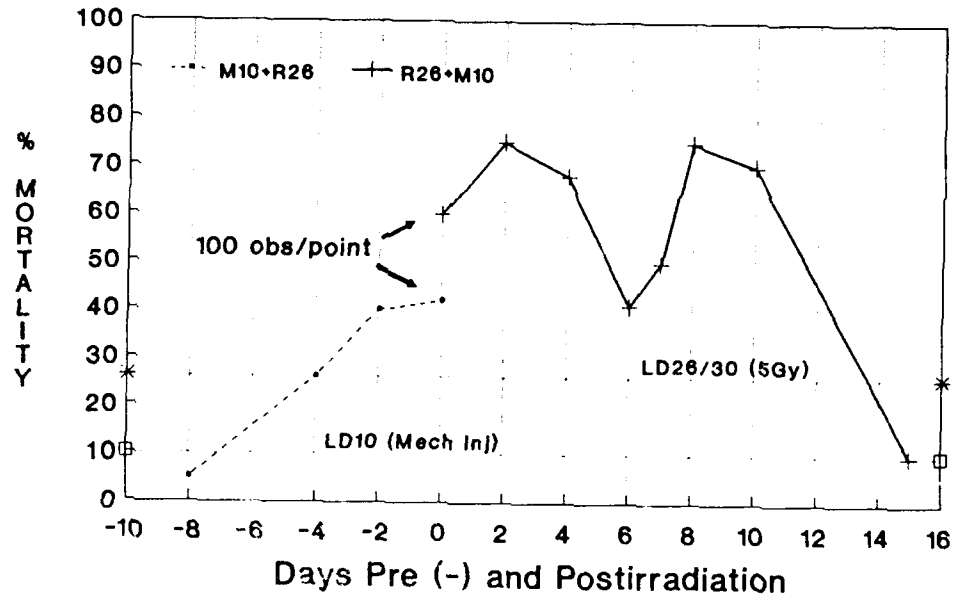
The exposure of swine to 50-psi reflected pressure in a shock tube resulted in 30 pct lethality, and unilateral exposure of similar animals to 400 R of neutron-gamma radiation was sublethal. When another group of swine was subjected to both stresses on the same day, a 33 pct mortality was observed; deaths were within 3 hours of irradiation and were most likely caused by the blast. Thus, no appreciable increase in mortality from combined effect was observed (Ref. 166).

3.2 SECONDARY BLAST EFFECTS AND IONIZING RADIATION.

The combined effects of open wounds and radiation were studied by Messerschmidt et al. (Refs. 68, 74, 87-89) in Freiburg and Munich, Germany, by Stromberg et al. at Walter Reed Army Research Institute, Washington (Refs. 41, 145-147), and by Ledney et al. at the Armed Forces Radiobiology Research Institute (AFRRI), Bethesda (Refs. 75-79, 81). Figure 11 depicts the main findings in experiments using mice by the Messerschmidt group. The injury consisted of LD_{10} skin wounds (M_{10}) and LD_{26} X-irradiation (R_{26}). When the mice were given skin wounds 8 days prior to irradiation, mortality was reduced to 5 pct. This is an approximately 80 pct reduction in mortality from that obtained when mice are exposed to 5 Gy X-irradiation alone.

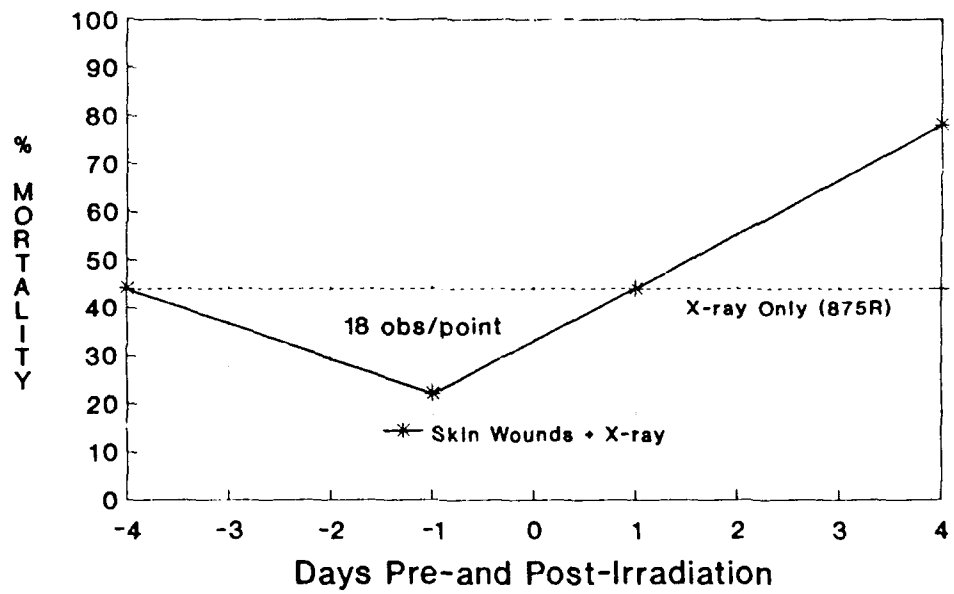
If the animals were subjected to the skin wounds 4 days before irradiation, the mortality is equivalent to that from irradiation only (figure 11). Skin wounds given 2 days before irradiation or on the same day before irradiation produced an additive effect on mortality compared with that from irradiation alone; the resultant mortality was approximately 40 pct. However, when an LD_{26} irradiation was given first, followed on the same day by an LD_{10} skin wound, a synergistic increase in mortality to approximately 60 pct was observed. This synergism reached a maximum of 75 pct when the LD_{10} skin wound was inflicted two days after irradiation, and the synergism persisted through day 5 after irradiation. A decrease to an additive effect of 40 pct mortality was noted on day 6, which was followed by synergistic increases in mortality when the mice were subjected to skin wounds on days 7 to 10. A return to normal values was seen by day 15.

One suspects that a skin wound sustained 8 days prior to irradiation stimulates hematopoiesis to higher activity which in turn increases the resistance against the deleterious effects of ionizing radiation. Messerschmidt et al. (Ref. 87), Koslowski (Ref. 68), and Langendorf (Ref. 74) suggest that the synergistic increase in mortality resulting from combined injury of X-irradiation and subsequent skin wounds observed during the first 5 days postirradiation is primarily caused by shock.



Data from reference 68 (1965)

Figure 11. Effect of time of mechanical injury on mortality due to combined mechanical and radiation injury.



Data from reference 145 (1968)

Figure 12. Effect of time of skin wound on mortality due to combined skin wound and radiation injury.

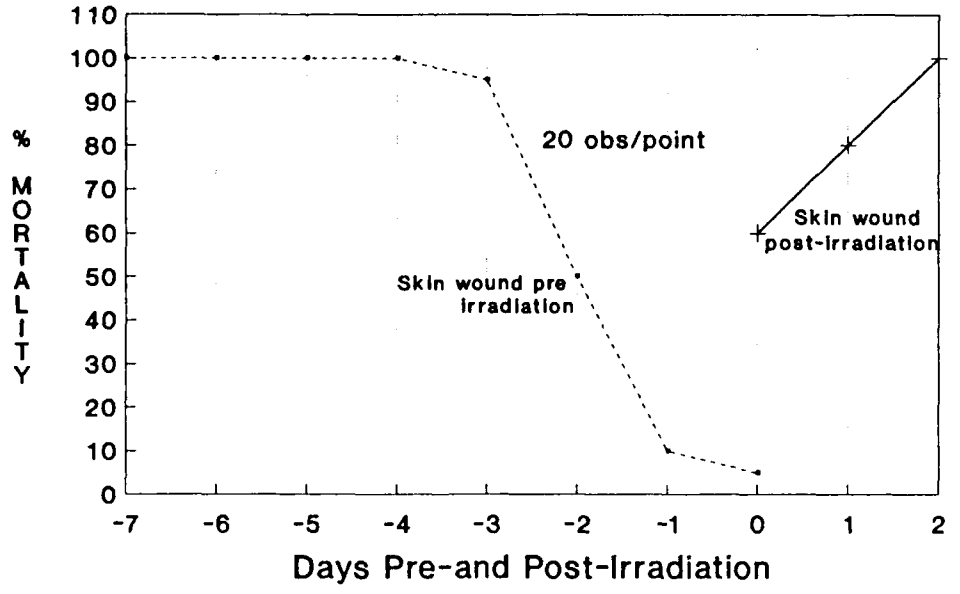
This effect may be similar to what was noted by Alpen et al. after burn (Ref. 5), although shock in the combined injury of burn and radiation was apparently caused mainly by burn (Ref. 5). Increased mortality when mice received their skin wounds between days 7 and 10 postirradiation was probably due to bone marrow injury (Ref. 68). In this case thrombocytopenia may induce increased bleeding of the skin-wounds, and granulopenia may decrease the ability to fight infection.

Stromberg et al. (Refs. 41, 145, 146) conducted similar experiments with male Walter Reed rats. They also observed that the timing of irradiation and the wounding had a definite effect upon mortality. Whereas wounding alone in their experiment produced no deaths, irradiation alone resulted in eight deaths out of 18 animals or 44 pct (figure 12). Wounding four days before irradiation or one day after irradiation did not alter the mortality rate from that of rats that were irradiated only. The radiation exposure of 875 R employed in this study is known to cause considerable damage to the bone marrow stem cells and precursor cells (Refs. 7, 43, 80). When the rats were wounded 4 days after irradiation, a synergistic increase in mortality to nearly 80 pct occurred. This increase was a result of reduced hematopoiesis due to the radiation injury and subsequent reduction in the protection against infection. This would have facilitated bacterial invasion from the skin wound to the blood resulting in septicemia. On the other hand, wounding one day prior to irradiation may have stimulated the hematopoietic feedback system to increase bloodcell production and to compensate for the destructive effects of ionizing radiation. Hence, the mortality was 21 pct instead of 44 pct (figure 12).

Ledney et al. (Ref. 75) conducted an experiment in which female mice were exposed to a dose of 9 Gy ^{60}Co gamma radiation, nearly 100 pct lethal. Different groups of these animals were given 4-pct skin surface wounds under light methoxyflurane anesthesia either on days 7 to 0 before irradiation or 0 to 2 days after irradiation. Figure 13 shows that wounding on days 7 to 3 prior to irradiation did not change the mortality due to irradiation; however, subjecting the mice to skin-wounds on day 2 before gamma radiation exposure reduced mortality to approximately 50 pct. Mortality

was further reduced to 10 pct or 5 pct when wounding occurred one day before or on the day of irradiation, respectively.

When the animals were wounded immediately after irradiation, the reduction in mortality was only to 62 pct. Wounding one day after irradiation did not significantly alter mortality when compared with that of the irradiated controls. It is assumed that mice wounded two days after irradiation died primarily from radiation injuries, because beyond 3 days postirradiation, bone marrow replacement of white cells is reduced and the protection against bacterial invasion is compromised.



Data from reference 75 (1985)

Figure 13. Effect of time of wound on mortality of wounded ^{60}Co irradiated mice.

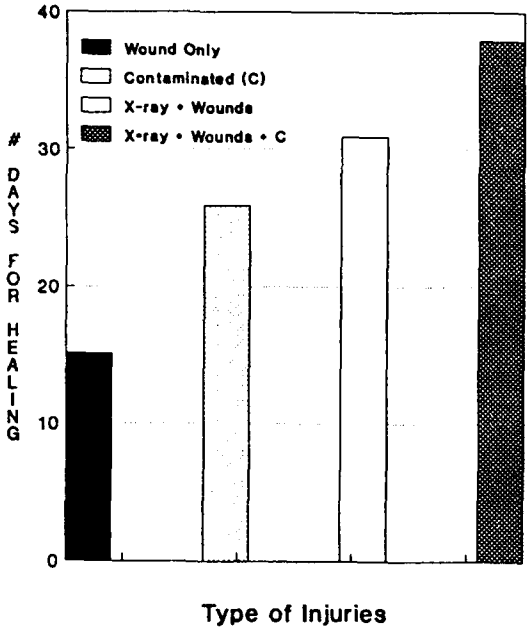
The authors proposed that strategically timed wound trauma would result in a significant increase in the number of mice surviving lethal irradiation. They further noted that such increases were always accompanied by increased endogenous spleen colonies in the irradiated animals, which indicates blood cell production.

Similar results were obtained earlier by Trott and Messerschmidt (Refs. 90, 154). Important factors that must be considered in the interpretation of the data are bacterial contamination of wounds and the physiology leading to survival or death. Since irradiation depletes the antimicrobial defenses of the host, it is possible that wounding after exposure to radiation provides a portal of entry into the immune-compromised host in addition to bacteria entering from the damaged gut. This might explain the 100-pct mortality when animals are wounded two days after irradiation. Wounding prior to irradiation may activate antibacterial defense since the hematopoietic system has not yet been damaged or destroyed. A 50-pct increase in peripheral blood granulocyte numbers was observed 1-2 days after wound trauma. Furthermore, histologic examination of the wound site indicated granulocyte and macrophage infiltration into the margin of the wound (Ref. 75).

The open wounds, hemorrhaging, and possibility of infection and contamination by radioactive materials are an important consideration in secondary blast effects and the nuclear environment. Several Russian experimenters have reported that small exposures of ionizing radiation enhanced wound healing (Refs. 59, 60, 91). However, these reports were not supported by the findings of Poljakov (Ref. 109). All workers agreed that continued exposure to low dose rate radiation eventually has the same effect as one large dose given in a relatively short period, and high doses and dose rates have a very detrimental effect on wounds as has been demonstrated experimentally and clinically (Ref. 33); in all cases they cause a delay in the healing of wounds. Exposure of wounds in rabbits to high doses of Polonium (alpha-particles) prolonged the time of their healing (Refs. 59, 60).

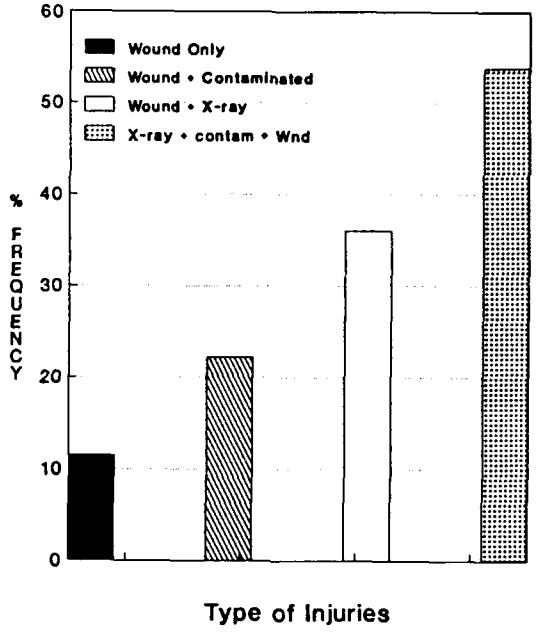
In another experiment with rabbits, Mariev (Ref. 85) demonstrated that while healing of wounds inflicted during the latent period after irradiation was nearly normal, it was severely delayed when wounding occurred during the manifest illness period. The authors conclude that necessary surgery must be completed very early after irradiation. When wounding occurs at the most symptomatic period of the radiation disease, a serious dystrophic process develops in the wounds since the epithelial cells are particularly radiosensitive. The cells in the wound surface undergo a degenerative necrobiotic and necrotic process. The proliferation of the cells is greatly reduced. The cells of the germ anlagen and the fibroblasts do not completely recover before 1.5 to 2 months. Inflammations and immunological reactions are very weak, and sometimes are not observed at all (Refs. 9, 51, 153). When recovery commences in surviving animals, immune reactions are again observed, necrotic tissue is removed, and new cells are produced (Refs. 110, 138). However, the time for healing of bullet wounds in irradiated rabbits was increased by 50 pct (Refs. 33, 124).

As the radiation dose increases, the prodromal and latent periods become shorter. The authors suggest that the best time for surgical care of wounds is six hours after wounding and irradiation (Refs. 85, 138) after which chances for infection increase rapidly. While surgical care during the prodromal and latent periods does not affect the healing of wounds, during the manifest illness period such care would appear to affect the outcome negatively. Korcanov (Ref. 67) showed that antibiotics decrease or may even prevent infections in these cases. Figure 14 depicts the increased number of days for healing, which is about 15 days for abdominal wounds alone, doubles for combined radiation injury, and increases further if the wounds are contaminated with radioactive materials (Ref. 33). Figure 15 indicates that the frequency of infection in abdominal wounds is three times greater in irradiated rats and five times greater if the wound area is also contaminated with radioactive materials (Refs. 24, 34, 42, 117, 131).



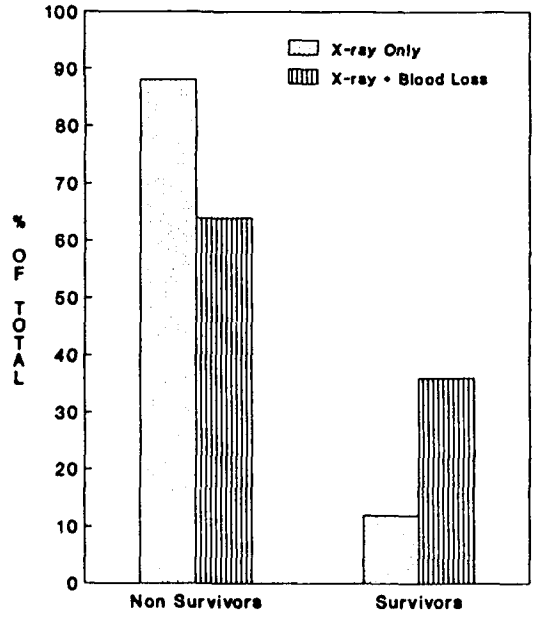
Data from reference 33 (1964)

Figure 14. Effect of radioactive contamination, X-ray and wounding on healing.



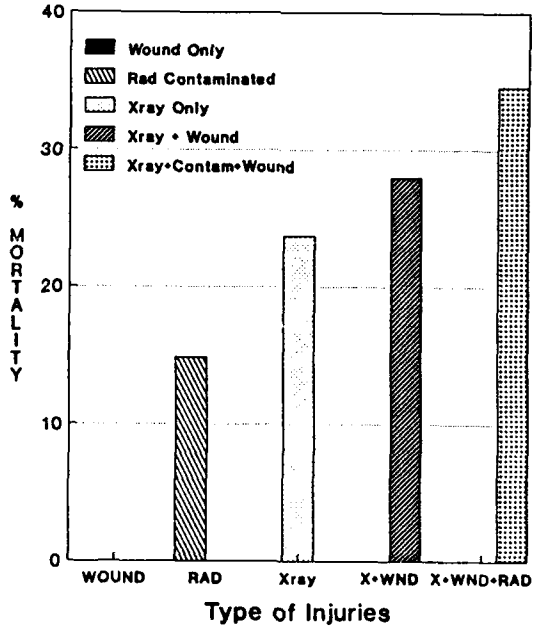
Data from reference 33 (1964)

Figure 15. Frequency of infections in abdominal wounds of irradiated rats.



Data from reference 31 (1956)

Figure 16. Effect on mortality of small blood loss 60-90 min post-irradiation.



Data from reference 33 (1964)

Figure 17. Effect of wounds, X-ray and radioactive contamination on mortality.

We have learned from animal experiments (Ref. 39) that the likelihood of hemorrhage will make it difficult to treat irradiated patients from 3-9 days to 45-50 days postirradiation depending on the radiation dose.

Hemorrhage was observed in Japanese situated 1.5 to 3 km from the epicenter of the bomb (Ref. 33). The hemorrhagic condition threatens survival of animals and humans, and complicates surgery. Loss of blood in addition to subsequent shock condition in animals with combined radiation injury will often cause deaths after postirradiation operations (Refs. 98, 151). Furthermore, irradiated animals are very sensitive to blood losses at specific periods after irradiation as shown by Praveckij (Ref. 111) who observed that the loss of 20 pct of the circulating blood 15-30 minutes after irradiation increased the severity of the radiation disease and elevated lethalities by 25 pct. All irradiated dogs that lost 40 pct of the total blood volume died.

On the other hand, as long as the radiation injury is limited to the bone marrow, small losses of blood immediately before or after irradiation may counteract its deleterious effects. This was demonstrated by Cerkasov (Ref. 31) who induced small blood losses in rodents 60-90 minutes after irradiation (figure 16). Without phlebotomy, his rodents sustained an $LD_{88/30}$. In bled animals this was reduced to an $LD_{64/30}$. Additional experiments by other investigators (Ref. 33) determined that the best resistance against radiation damage is obtained when small bleeding occurs 4-5 days before irradiation. A small blood loss would stimulate increased hematopoiesis and increase the number of white cells and immune protection. However, when blood loss occurs during the manifest illness phase, it increases the severity of the illness, and animals might die during the phlebotomy. They conclude that special care must be taken in the timing of surgery with combined injuries, because of blood losses. Berkutov et al. (Ref. 18) determined that 12 pct of dogs subjected to combined injuries die of secondary blood loss.

Figure 17 depicts the effects of sublethal skin wounds, radioactive contamination and LD_{24} irradiation in rats (Ref. 33). Berkutov reported that dogs that were subjected to combined injuries (radiation plus wounding) and not treated with antibiotics developed the most sensitive anerobic wound infections (Ref. 17). Irradiated and infected dogs when untreated, showed 100-pct lethality in these studies.

Mortality from the extreme putrid wound infections (Refs. 42, 131) was shown to be reduced with antibiotic treatment.

3.3 TERTIARY BLAST EFFECTS AND IONIZING RADIATION

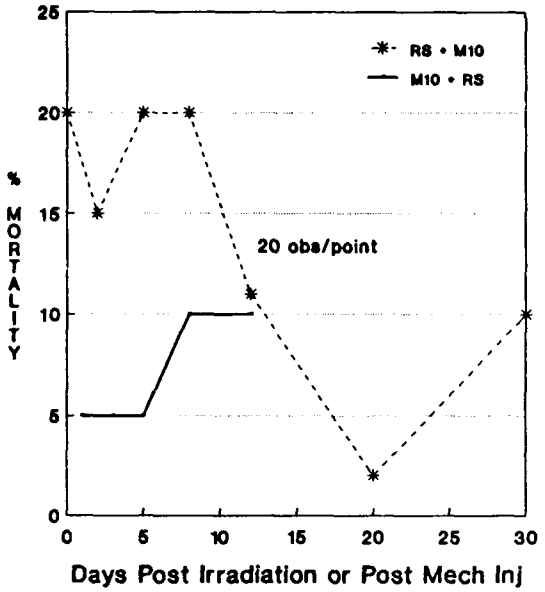
3.3.1 Animal Experiments with the Noble-Collip Drum.

Schildt (Ref. 127) studied the combined effect of radiation and mechanical injury using methods described in prior publications (Ref. 128, 129). Mice were subjected to that number of turns of the Noble-Collip drum that was either sublethal (LD_S) or LD_{10}. LD_S was defined as one half the number required for $LD_{50/30}$. The time interval between traumas was varied between 0 to 30 days. The following symbols were used:

M_S = sublethal drum trauma
M_{10} = 10-pct drum trauma lethality
R_S = sublethal radiation
R_{10} = 10-pct radiation lethality

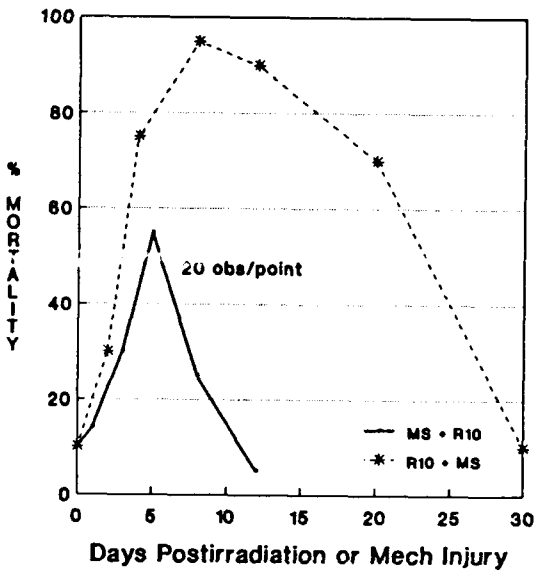
The symbol of the trauma that appears first was administered first.

Figure 18A shows that sublethal radiation in combination with M_{10} causes at best an additive effect. This occurs whether radiation is given first or last. For example, the maximum increase in mortality for R_S+M_{10} or $M_{10}+R_S$ is only 20 pct (figure 18A). Clearly, a sublethal radiation dose with only moderate injury to bone marrow does not result in a synergistic increase in mortality.



Data from reference 127 (1972)

Figure 18A



Data from reference 127 (1972)

Figure 18B

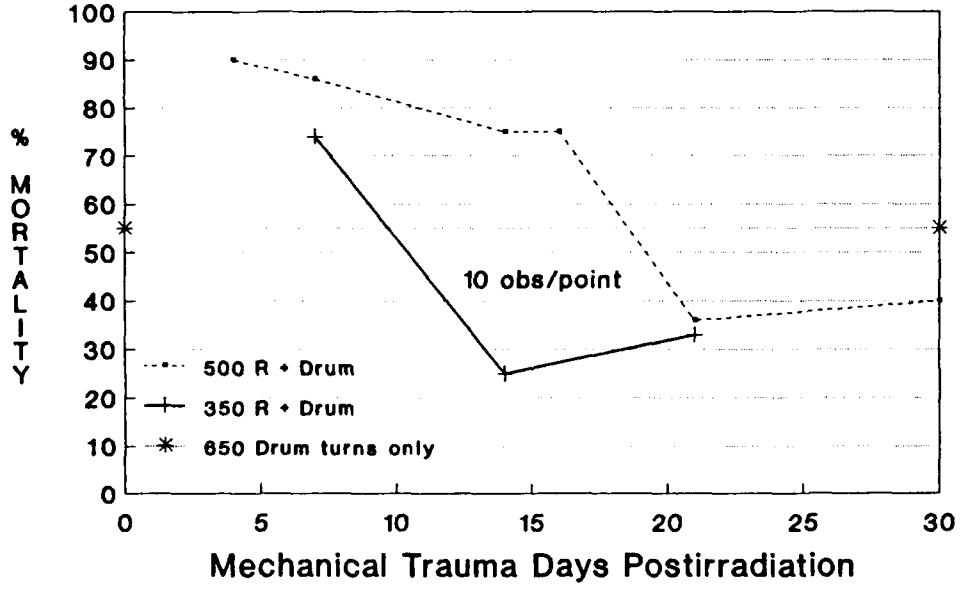
Figure 18. The effect of various sequential combinations of sublethal and LD_{10} mechanical and radiation injury on rat mortality.

Figure 18B shows that R_{10}, particularly if it was given to animals first, resulted in synergistic increases in mortality. Animals subjected to R_{10} first and subsequently to M_S from days 2 to 21 resulted in mortalities between 75 and 100 pct. When the rats were stressed with M_S first (figure 18B) and R_{10} five days later, a synergistic increase in mortality to 55 pct was observed. The higher increase between days 2 and 21 when R_{10} is given first probably was the result of greatly reduced number of granulocytes and macrophages caused by earlier radiation-induced bone marrow cellular damage, which compromised the defense against bacteria invading the injury.

Experiments by McKenna and Zweifach (Ref. 86) used a combination of X-ray exposures (sublethal, LD_{50} and LD_{100}) and trauma from the Noble-Collip drum (Ref. 100). These experiments showed that total body irradiation predisposed the rat to subsequent traumatic shock after being tumbled. Figures 19 and 20 graph the data obtained from these studies.

Baseline data on mortality from drum shock were established by sub-

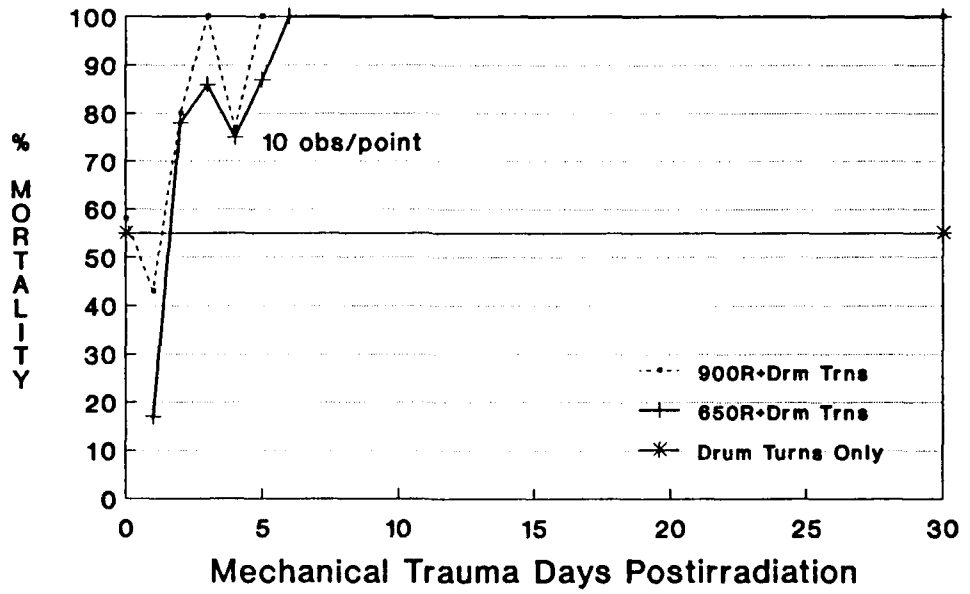
jecting random batches of rats to 650 (LD_{55}) and 700 (LD_{65}) turns at 40 rpm in the drum. The rats were carried upward with each revolution of the Noble-Collip drum and then fell, thereby receiving widespread body trauma. In the first study, rats were exposed to sublethal exposures of either 350 or 500 R of X-rays and subsequently subjected to drum trauma. Figure 19 indicates that X-irradiation predisposed the animal to subsequent traumatic shock. This predisposition is seen in groups tumbled up to 7 days after exposure to 350 R and in groups tumbled as late as 16 days after 500 R. After that, the 350 R rats showed recovery and resistance to trauma up to 21 days, and the 500 R animals, from day 21 to 30.



Data from reference 86 (1957)

Figure 19. Effect of sublethal radiation and subsequent mechanical trauma on rat mortality.

Figure 20 shows that survivors of 650 R and 900 R X-rays remained highly susceptible to drum trauma for periods up to 30 days postirradiation. With 650 R ($LD_{50/30}$) the impairment of the shock defense mechanism became evident only after 3 to 4 days; with 900 R ($LD_{100/30}$) impairment occurred sooner (figure 20). Gross and microscopic examination of the tissues showed the effects of post-traumatic shock. Bacterial contamination was not seen in normal rats subjected to drum shock; however, after drum trauma, X-irradiated rats showed varying degrees of bacterial contamination, chiefly of a Pseudomonas aeruginosa type. Comparable bacterial contamination was seen in rats after X-irradiation alone.



Data from reference 86 (1957)

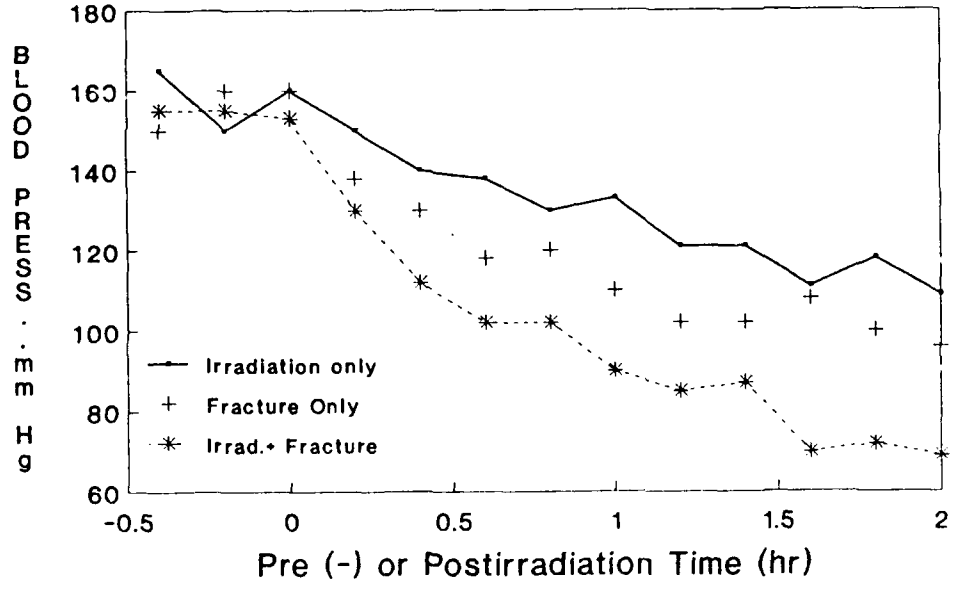
Figure 20. Effect of lethal radiation and subsequent mechanical trauma on rat mortality.

From these experiments (figures 19, 20 and Ref. 86), it appears that total body X-irradiation can exert a major effect on the subsequent capacity of the organism to withstand trauma. A predisposition to shock becomes apparent within 3 to 4 days postirradiation and persists thereafter for varied amounts of time depending on the X-ray exposure levels. When the exposure reaches the 50% or greater lethality level, shock is poorly tolerated. The authors suggested that since susceptibility to trauma begins to appear at the time that intestinal pathology becomes prominent, that condition may have reduced the tolerance for shock. However, in $LD_{50/30}$ irradiated animals, survival did not decrease drastically until after 7-9 days after irradiation, and the animals showed only minor pathology in the gastrointestinal tract. Although infection per se did not represent a major contributing factor in the predisposition to trauma following X-ray exposure, the authors did not rule out unusual susceptibility to bacterial endotoxin or tissue by-products and cited supporting evidence for it (Ref. 137).

Several Russian investigators reported that animals subjected to combined injuries often exhibit a shock condition (Refs. 33, 67, 98, 170). These investigators suggest that ionizing radiation affects the functional capability of the central nervous system, which would explain the rapid decrease in blood pressure soon after exposure to ionizing radiation (figure 21). Decreases in blood pressure within 8 minutes were also reported for the monkey (*Macaca Mulatta)* receiving 2500 rads of pulsed mixed gamma-neutron radiation (Ref. 157) and beagles subjected to a midline tissue dose of 19000 rads of pulsed gamma-neutron radiation to the trunk and 14,000 rads to the head (Ref. 155). A relationship was observed between dose rate, decrease in blood pressure, and performance in monkeys receiving 1000 rad of ^{60}Co gamma radiation (Ref. 27). The thresholds were approximately 300 rad at dose rate of 25 rads per minute. Upper body irradiation of patients with 800 rad (10-MeV linear accelerator at dose rates of 30-40 rad/min) induced nausea, vomiting, increases in temperature and pulse rate and a drop in blood pressure. The onset of this syndrome occurred shortly after the procedure and lasted for up to 10 hours (Ref. 123).

Other studies (Ref. 120) have shown changes in blood pressure during irradiation of a number of patients. Systolic levels were lowered an average of 30 mm Hg and diastolic pressure by 5 to 8 mm Hg with the maximum depression reached at the same time as the height of the skin reaction to the radiation.

The only data on the drop in blood pressure following combined injury is that reported for the combination of bone fracture and radiation in animals reported by Korcanov et al. (Ref. 67) as quoted by Chromov (Ref. 33). Figure 21 shows a further decrease in blood pressure after combined injury as compared with exposure to radiation only.



Data from reference 67 (1958)

Figure 21. Blood pressure after irradiation, fracture and combined injury.

Unfortunately, the original graph presented in reference 33 did not show the time postirradiation during which the decrease in blood pressure occurred. However, based on the other reports (Refs. 27, 120, 123) one can assume that the onset occurred shortly after the completion of irradiation and continued for two hours as shown in figure 21 of this report.

Korcanov (Ref. 67) tells us that the hypotonic condition may lead rapidly to severe shock. Furthermore, soon after exposure to ionizing radiation, the concentration of histamine in the circulation is greatly increased (Refs. 14, 55). Gorizontov (Ref. 55) injected blood from head-irradiated dogs into normal unirradiated animals, and found a significant decrease in blood pressure of the normal dogs. American investigators who studied plasmas from dogs exposed to radiation from atom bombs found that the depressing effect on the blood pressure was caused by ferritin which is produced in the liver (Ref. 165). The Russian authors further suggested that the psychological effect from being exposed to atom bombs may contribute to the ensuing shock condition.

The Russian authors concluded that the irradiation induced injuries to physiological protective mechanisms of the central nervous system, and that the humoral changes (blood pressure drop) and the psychic traumas led to increased sensitivity to subsequent traumas and eventually to shock. This was demonstrated by greatly increased shock incidence and earlier appearance of symptoms in rabbits exposed to 800 R X-rays in addition to fractures of the upper femur (Ref. 99).

3.3.2 Combined Injury of Bone Fractures and Radiation.

G. W. LeRoy reported (Ref. 82) that at least 11 pct of the Hiroshima and Nagasaki victims who suffered mechanical injuries also incurred bone fractures and for many this was combined with radiation injury from the atomic bombs. Most of our current knowledge about combined injuries of bone fractures and ionizing radiation was obtained by observing bone healing in irradiated animals (Ref. 61, 62, 168):

1. Regeneration time of fractures is prolonged, particularly during the manifest illness period.

2. In sublethally irradiated animals, the consolidation of open fractures occurs between days 45 and 60. This may be compared to days 30-40 in nonirradiated controls (Refs. 61, 62, 168).

3. Some animals developed a pseudoarthrosis at the point of the fractures.

Tracenko (Ref. 152) reported healing of fractures in normal animals at about 6 weeks, and mending of similar fractures in irradiated animals at a minimum of 10 weeks. Healing of bone fractures was further delayed if the fracture occurred during the manifest illness period (Ref. 140). Furthermore, the effects of radiation were much more severe and more rabbits died earlier if animals received bone fractures during the manifest illness period (Ref. 65). The time required for fractures in irradiated animals to heal increased as the amount of the exposure increased. Rubinstejn (Ref. 121) demonstrated that the consolidation of fractures in dogs subjected to low exposure radiation was practically identical to that in unirradiated animals, although higher exposures resulted in much slower regeneration and recovery. Ivanov (Ref. 60) observed first signs of bone consolidation in healing of fractures of rabbits by day 7 and full consolidation by the 35th day. In animals exposed to 600 R X-rays, the first signs of consolidation are not seen until the tenth to fifteenth day, and full consolidation by day 50 to 55.

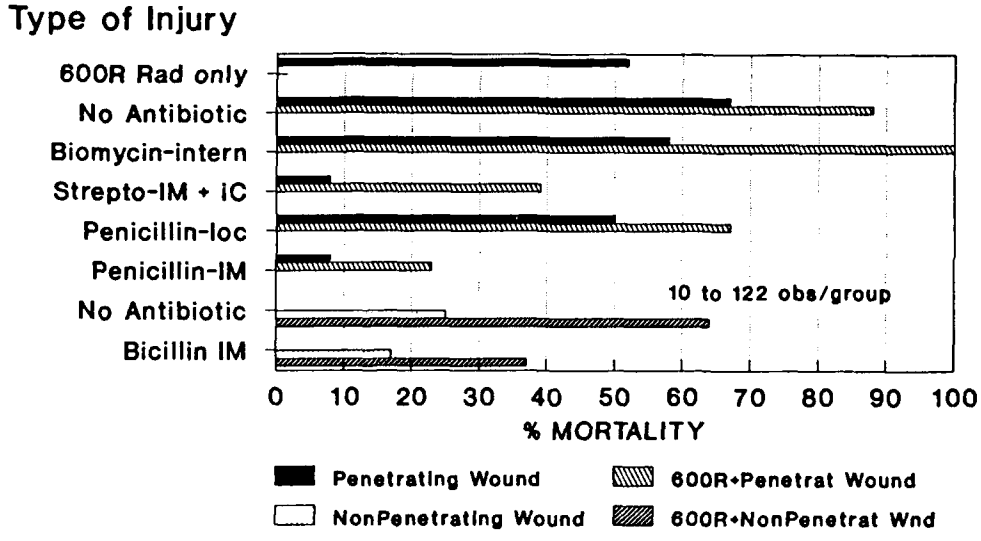
Sarkisov(Ref. 124) reported that ionizing radiation increased the severity of fractures due to gun shot wounds and caused the development of sepsis. The consolidation of gunshot fractures in irradiated rabbits started much later than in unirradiated animals. The consolidation of an open gun shot fracture of the upper femur was delayed by one month in sublethally irradiated rabbits. He also reported that even closed fractures can be infected during the radiation-induced leukopenia. Krupko (Ref. 71) reported an increase in lethality in irradiated rabbits with bone fractures (Table 3). The combination of fractures, burns, and radiation

increased further the severity of the injury and subsequent lethality (Ref. 72). He recommend that a prolonged rest period with restricted movements of the injured extremity accompany appropriate medical treatment for combined injury of fractures plus radiation.

Table 3. Mortality of rabbits receiving radiation and bone fractures (from Ref. 71)

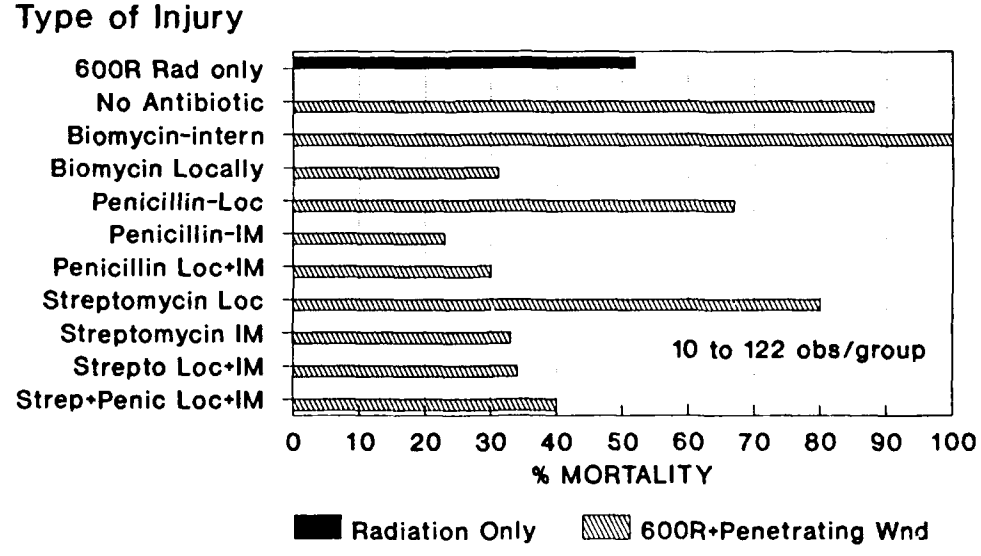
	Mortality (percent)
1. Radiation	16
2. Radiation & uncomplicated fracture	50
3. Radiation & open fracture	85

Figures 22A and 22B depict the results of a series of experiments on "lesions of the skull and brain in acute radiation sickness" (Ref. 3). This study used 814 rabbits that were subjected to the combined injury of 600 R X-rays and, immediately thereafter, penetrating cranial and cerebral wounds. The rabbits received penetrating cranial wounds involving opening of the meninges and damaging of a section of cerebral matter 3-5 mm in diameter. Bone fragments were introduced into the meningocerebral wound, and the wound was contaminated with sterile earth and infected with a 24-hour culture of pathogenic hemolytic Staphylococcus aureus or a mixture of this culture with a culture of pathogenic hemolytic streptococcus. The type of injuries and radiation exposure as well as the various forms of treatments are shown in figures 22A and 22B.



Data from reference 3 (1962)

Figure 22A



Data from reference 3 (1962)

Figure 22B

Figure 22. Mortality of rabbits receiving penetrating and nonpenetrating skull wounds, irradiation, and antibiotics in various combinations.

The following basic conclusions were made by the experimenters:

(1) In combination with radiation sickness caused by penetrating radiation, wounds of the skull and brain become particularly severe, and, they, in turn, aggravate the course of acute radiation sickness itself.

(2) As a result of the weakening of the protective forces of the organism caused by the combined injuries, infectious complications of the wound, pneumonia and other infectious processes often develop. Therefore, careful surgical treatment of the wound as well as early and systematic use of antibiotics are much more important in these injuries than in ordinary wounds.

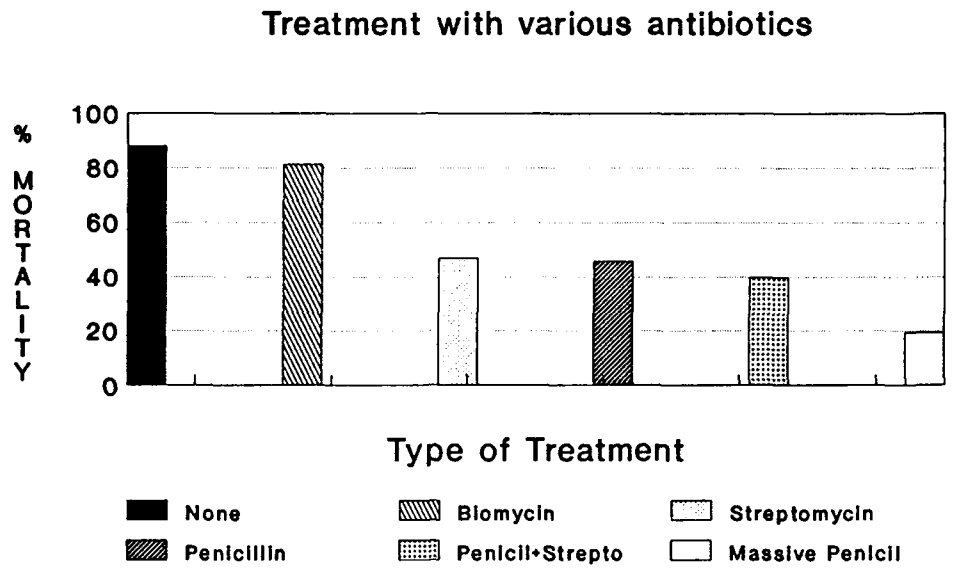
(3) Infectious complications that develop in rabbits with these combined injuries are, as a rule, not associated with an increase in leukocyte count in the peripheral blood during the height of radiation sickness, and during this period intracranial infectious processes are not ordinarily accompanied by any detectable increase in the number of cellular elements in the spinal fluid.

(4) The most effective antibiotics for these injuries are mixtures of penicillin and streptomycin or large doses of penicillin. The most effective treatment is a combination of intramuscular injections of antibiotics and application of them to the wound itself or injection into the subarachnoid space (figures 23 and 24). The use of biomycin administered orally is not effective as it penetrates poorly into the spinal fluid and the brain (figure 23).

(5) Intramuscular injection of penicillin or bicillin for the combinations of acute radiation sickness with nonpenetrating wounds of the skull was effective.

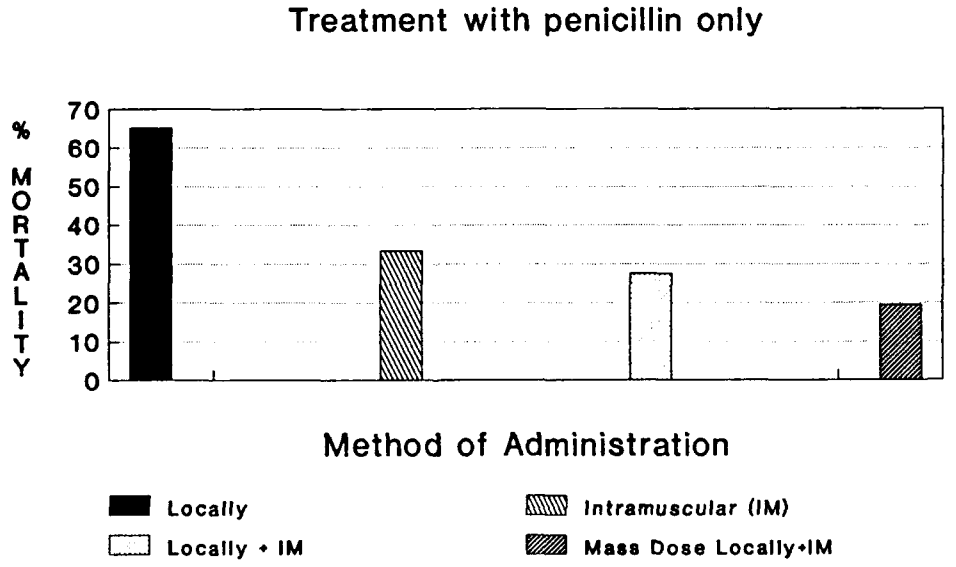
(6) The presence of an open wound of the skull or brain in animals exposed to ionizing radiation favors the development of infectious complications and increases mortality; hence, such wounds should be closed.

(7) The overwhelming majority of experimental animals that were irradiated and that had contaminated, infected skull wounds survived, and the wounds healed when appropriate antibiotics were administered and the wound was sutured within three days.



Data from reference 3 (1962)

Figure 23. Mortality of animals with combined injury treated with various antibiotics.



Data from reference 3 (1962)

Figure 24. Effect of method of administration of penicillin on mortality of cerebrally wounded and irradiated rats.

Some Russian reports indicate that small exposures to ionizing radiation stimulate bone tissue growth and accelerate the healing of fractures (Refs. 60, 69, 97, 132, 142). This principle is used in the treatment of fractures and osteomyelitis. However, continuous exposures to small doses of radiation for long periods may induce bone cancers (Refs. 73, 155) and eventually have the same effect as large exposures given in a short period; viz., decalcification, atrophy, osteoporosis, and even necrosis of the bones (Refs. 1, 16, 96, 144, 158). Pathological effects also occur in the matrix, which results in a thinning of the cortex of the long bones, a disturbance of new lamella formation of bone, and in an enlargement of the lumen of the haversian canal. Pavlova (Ref. 103) observed radiation damage to the osteoblasts, the vascular circulation of bone and the bone marrow including degenerative and necrotic changes of the bone marrow cells. The author also report a disturbance of the calcium exchange of bone, which eventually leads to increased spontaneous fractures (Ref. 103).

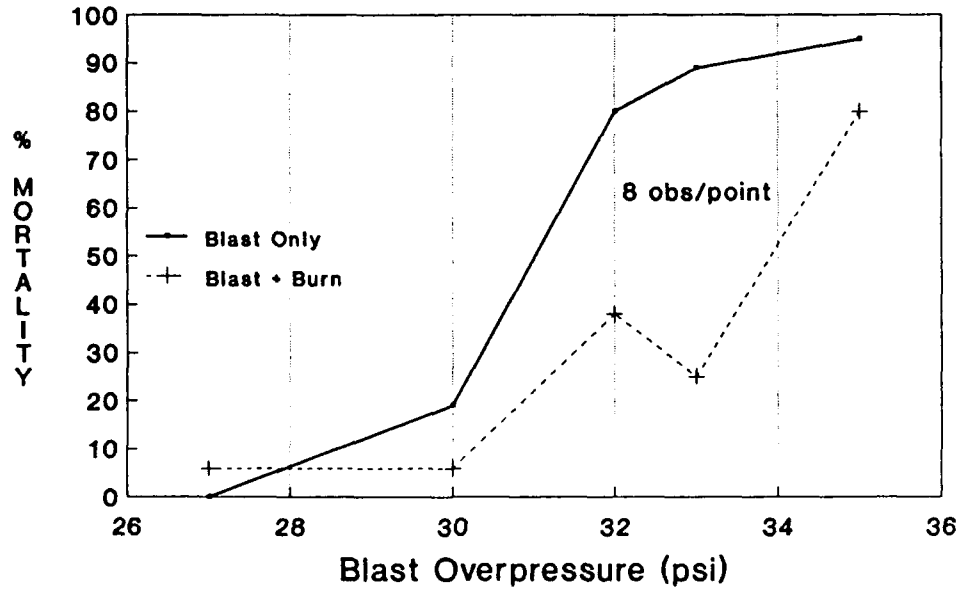
Particularly damaging to the bone is the incorporation of bone-seeking radioisotopes (strontium, plutonium, radium, phosphorus, calcium, thorium, yttrium, barium). K. Z. Morgan (Ref. 92) determined that of injected radioisotopes that were incorporated into bone, 45-60 pct were radiothorium and yttrium, 45-60 pct strontium, and 60 to 80 pct plutonium and radium (Ref. 92). One half hour after administration of radiophosphorus in rats, one finds 18.3 pct muscles and 19.1 pct in bones. However, after 98 hours, the concentration in muscles was only 3.6 pct and that in the bone increased to 92 pct (Refs. 46, 57, 148).

SECTION 4

OTHER COMBINED INJURIES

4.1 BLAST AND THERMAL RADIATION.

In a study by Richmond and Pratt reported by Jones (Ref. 63), rats were subjected to blast in shock tubes and burns from tungsten-quartz lamps. Blast levels in the LD_{50} range were combined with nonlethal burns. Thermal energy levels of 6 cal/cm^2 were used to produce burns covering about 30 pct of the body surface area. The effect of blast pressure is shown in figure 25 (33 psi killed about 90 pct of the exposed rats). If those rats were subjected to nonlethal burns two hours prior to the blast, the 24 hour mortality was reduced to 25 pct (figure 25). It was not clear how the nonlethal burn interacted antagonistically with the LD_{90} blast to reduce mortality.



Data from reference 63 (1971)

Figure 25. Effect of 30% burn two hours prior to blast injury on 24 hour mortality of rats.

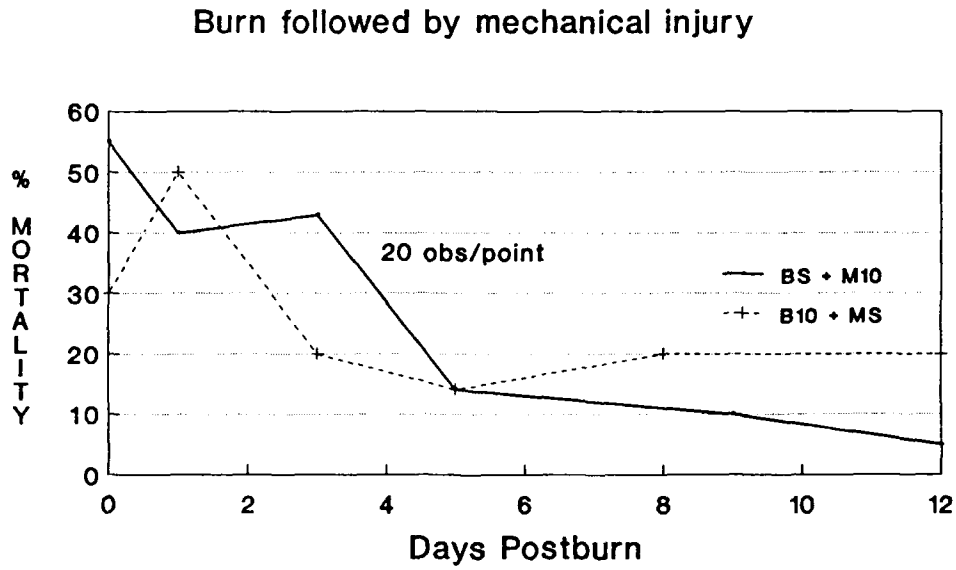
4.2 MECHANICAL INJURY AND THERMAL RADIATION

Zgenti (Ref. 169) found that persons with deep burns covering 20 pct of body area satisfactorily tolerated a 20 to 25 pct loss of blood volume, but that mortality increased with further losses of blood. The general condition and symptoms of traumatic shock appeared to be more pronounced with smaller burned areas in combination with moderate mechanical trauma than in cases of somewhat greater mechanical injury or burn alone (Ref. 169).

Schildt (Ref. 127) selected thermal injury (scald burn) and the Noble-Collip drum mechanical injury as combined injury components. In accordance with methods described in prior publications (Refs. 128, 129), standardized burns were determined which were sublethal, LD_S, or LD_{10}. The numbers of turns of the drum that either resulted in an LD_S or LD_{10} were also determined. The time interval between two traumas varied between 0 to 12 days for burn and drum trauma. The following symbols are used for the various traumas:

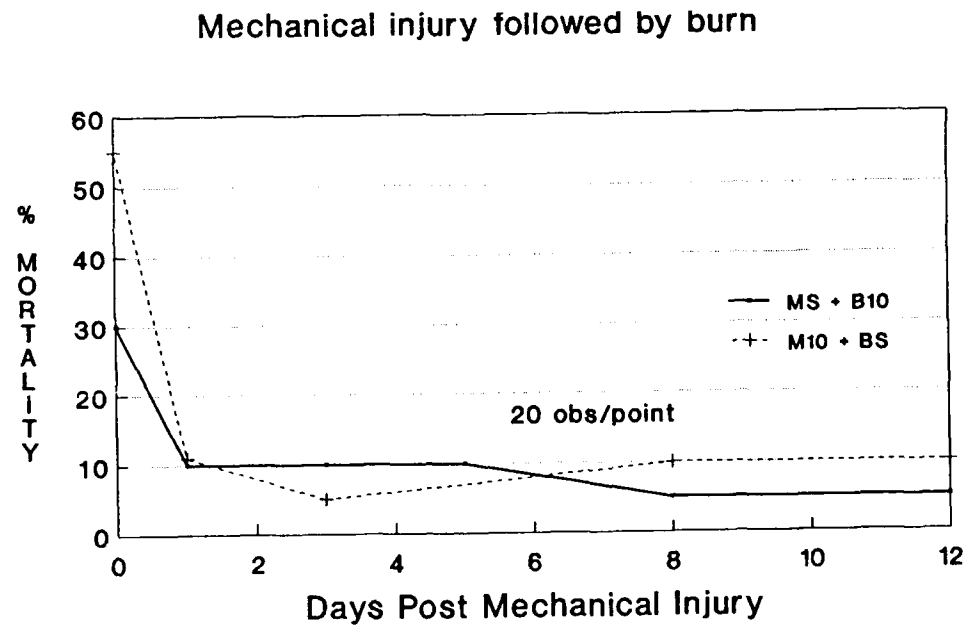
B_S = Sublethal burn
B_{10} = Burn that causes 10 pct lethality
M_S = Sublethal drum trauma
M_{10} = Drum trauma that causes 10 percent lethality

The symbol of the trauma that appears first was administered first. Figures 26A & 26B indicate that when mice were subjected on the same day to B_S+M_{10} or M_{10}+B_S, a synergistic increase in mortality to 55 pct occurred. Similar exposure on the same day to B_{10}+M_S and M_S+B_{10} resulted in 30-pct mortality. Subjecting the animals to traumas sequentially resulted in synergistic increases in mortality only when the animals were subjected to B_S first followed by M_{10} one or three days later, or B_{10} first and M_S one day later. The only significant increases in mortality occurred when the mice were subjected to drum trauma and to burns on the same day or when burns were first.



Data from reference 127 (1972)

Figure 26A



Data from reference 127 (1972)

Figure 26B

Figure 26. Effect of sublethal LD_{10} burn and mechanical injury on rat mortality.

4.3 BLAST, THERMAL RADIATION, AND IONIZING RADIATION

It has been reported that approximately 5 pct of the patients who survived the effects of nuclear explosions in Japan sustained blast, burn, and radiation injuries (Ref. 101). Richmond et al. at the Lovelace Foundation (reported in Ref. 166) conducted the only known study in which rats were subjected to all three of these stresses. The results of this study are shown in figure 27. The animals were subjected to a 250 rad exposure ($LD_{10/30}$) of nuclear radiation (mixed neutron-gamma), a 25 to 35 pct sublethal body surface area flash burn of 6 cal/cm^2, and an LD_5 dose of airblast in a shock tube. An additive effect from this combination should result in a mortality of about 15 pct. However, when all three stresses were combined on the same day, a 64 pct 30-day mortality was observed (figure 27). Only 5 pct of the animals died within 24 hours. If the burn and blast injuries occurred seven days after irradiation, a 24-hour mortality of 35 pct resulted which only increased to 41 pct by the day 30 post-trauma. Burn and blast injuries sustained fourteen days following nuclear irradiation resulted in a 20-pct 30-day mortality with only a few early deaths.

When the rats were subjected to 350 rad nuclear radiation ($LD_{50/30}$) on the same day with blasts and thermal injuries, the 30-day mortality increased to 94 pct (figure 27). It appears that exposure to three stresses on the same day raised mortality from 15 pct to a synergistic 64 pct. Most animals apparently died of injuries to the bone marrow further complicated by infections, although gut effects may also have been a factor. The $LD_{50/30}$ in rats is normally about 800 to 1000 rads gamma irradiation for bone marrow and is about the same for gut effects ($LD_{50/5}$=900 rads) (Ref. 21). However, the $LD_{50/30}$ for nuclear (combined gamma and neutron) radiation is reduced to about 400 rads, because of injury to the gut (Ref. 22). Gut injuries may have been involved in some of the early deaths when blasts and burns were also given on the day of irradiation in the Richmond study. Since gastrointestinal irradiation injuries do not contribute to mortalities beyond seven days postirradiation, deaths observed within 24 hours were probably caused by shock in response to all three stresses. When the rats were subjected to blast and burns fourteen days after irradiation,

only an additive rather than a synergistic effect of all three stresses was noted.

According to Russian investigators, low X-ray exposures by themselves do not induce the radiation sickness syndrome but will do so in combination with blasts. Zgenti et al. (Ref. 169) reported that ionizing radiation and blasts in combination with wounds or burns will increase the time for healing of wounds or burns.

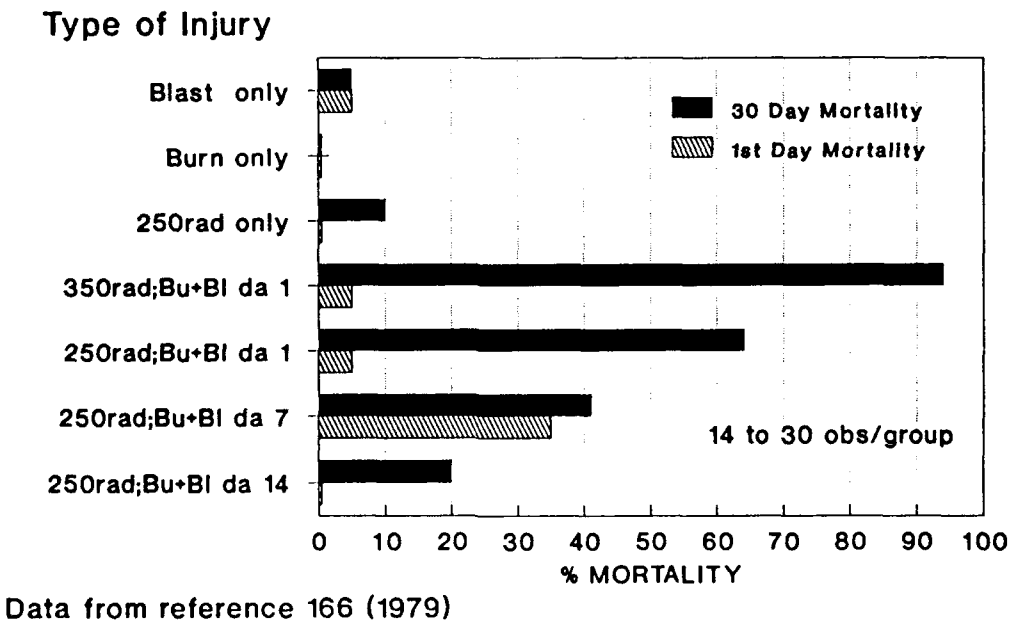
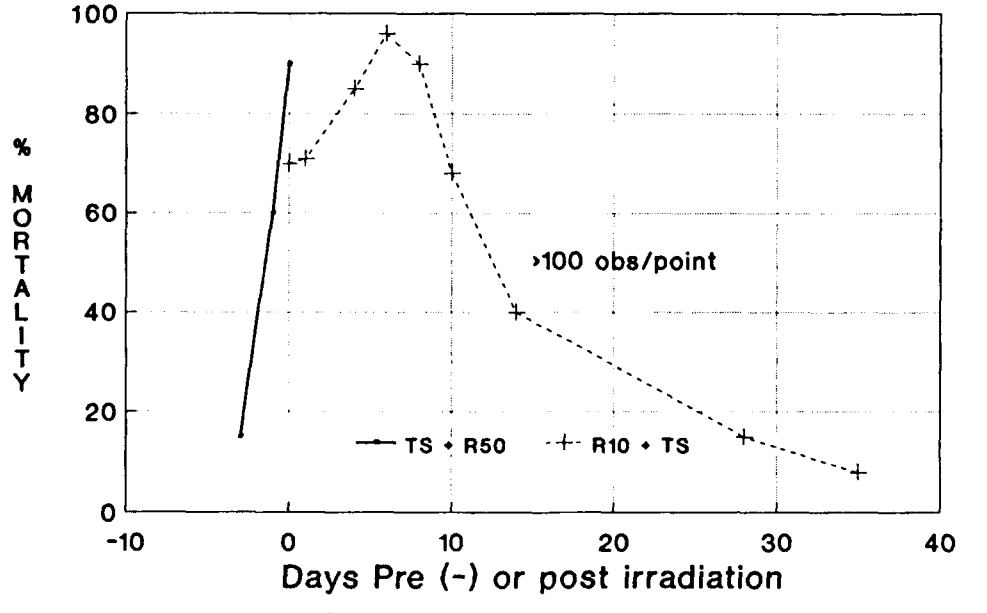


Figure 27. Effect of concurrent nuclear radiation, blast and burn on rat mortality

SECTION 5

INFECTION AND IONIZING RADIATION

Schildt et al. explain the pathophysiological responses occurring in combined injury in reference 130. CBA male mice were subjected to sublethal bacterial toxin (T_S) from Pasteurella pseudotuberculosis either up to 3 days prior to an LD_{50} radiation from X-rays (R_{50}) or up to 6 weeks postirradiation from an LD_{10} exposure (R_{10}). Figure 28 shows a decrease in lethality from 50 pct to 15 pct when the toxin is given three days before irradiation . When the bacterial toxin was administered intraperitonially one day preirradiation, the difference was not significant, however given at approximately the same time (the toxin first), a synergistic increase in mortality from 50 pct to 90 pct was observed. When the toxin was administered 2 to 10 days, postirradiation, a synergistic increase in mortality reached its maximum of 90 to 97 pct between days 6 to 8. Thereafter, a slow return to normal values occurred 4-6 weeks after irradiation.



Data from reference 130 (1968)

TS-Sublethal Toxin
R10-LD10/30; R50-LD50/30(X-ray)

Figure 28. Effect of various sequential combinations of LD_{10} and LD_{50} radiation and sublethal toxin on mortality of mice.

The increased number of postirradiation deaths in animals concurrently subjected to infectious agents had previously been ascribed to 1) increased permeability of skin surfaces and mucous membranes, 2) reduced numbers of granulocytes, (3) weakening of phagocytic activity of the reticuloendothelial system and 4) a reduced immune-capability (Refs. 15, 25, 30, 40). The authors ascribed the probable mechanism of the decrease in mortality when the toxin was given three days before irradiation to an unspecific increase in resistance as discussed in other reports (Refs. 53, 102, 127, 171). However, recent research in this area (Ref. 80) indicates that the specific response of the hematopoietic stem cells and precursor cells to the bacterial toxin results in an increase of active hematopoiesis and subsequent increased defense if the stress is administered prior to the ionizing radiation.

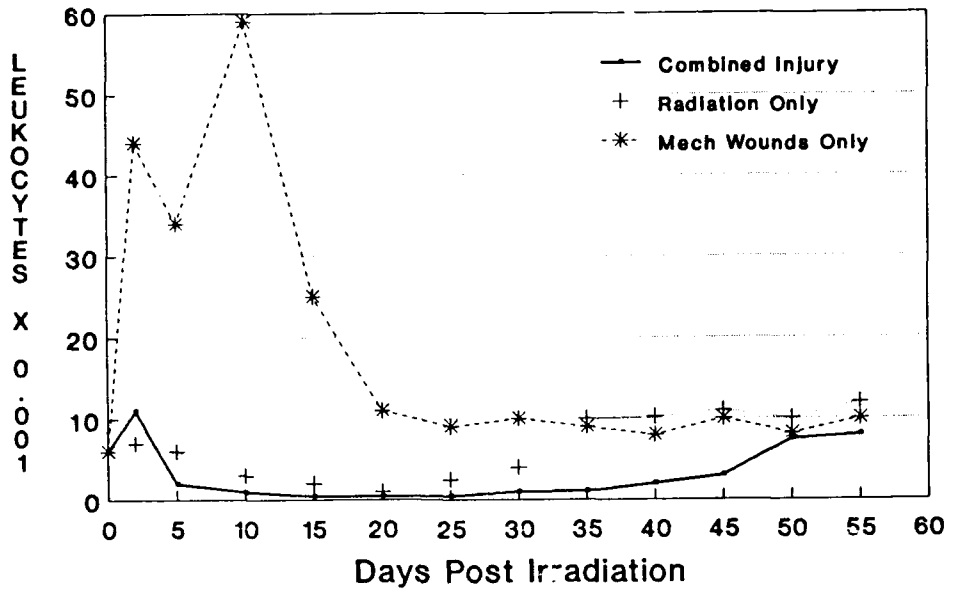
According to the authors, ionizing radiation presents a heavy burden on the defensive and compensating mechanisms of the body. When a second trauma hits the organism (bacterial toxin), very little defense can be mobilized thus resulting in a dramatically high mortality rate, since radiation drastically undermines the animals' defense against infection. When the animals are further subjected to the bacterial toxin between days 4 and 10 postirradiation, the decreased numbers of granulocytes, macrophages, and lymphocytes are no longer able to defend against the toxin, and a dramatic increase in mortality results.

The similarities of results in this study (figure 28) with those using burn or mechanical injuries in combination with radiation (figure 8 and 18) suggest that infection played an important role between days 8 and 20 postirradiation in both experiments.

Additional biological actions that have been considered are the release of bacterial endotoxin and the elevation of prostaglandin (PGE_2) levels. The two primary sources of endotoxin are the wound site and the intestine (Ref. 161). It has been shown that endotoxin given prior to irradiation can afford a degree of radioprotection; however, higher doses of endotoxin given after irradiation increase mortality (Ref. 162).

Prostaglandins are modulators of hematopoiesis, and elevated levels are seen after both traumas (Refs. 143, 163). As long as the bone marrow stem cells and precursor cells are intact, prostaglandin may enhance hematopoiesis and increase the defense against infection. However, in animals subjected to trauma after irradiation, increased concentrations of prostaglandins may result in death associated with sepsis (Ref. 135).

As soon as the devastating results of dropping the atom bombs on Hiroshima and Nagasaki became known, Russian investigators initiated a series of experiments to study the effects of combined radiation injury. They observed that thermal or mechanical trauma was usually accompanied by a greatly increased leukocytosis. This may be seen in figure 29 which shows the effects of abdominal gun shot wounds on peripheral leukocyte concentration in dogs (Refs. 54, 118, 138, 160). In response to the abdominal wounding a five- to sixfold increase in the leukocyte concentration may be noted for 14 days, which thereafter returns to normal. Such a leukocytosis is completely absent in dogs subjected to a high sublethal exposure of radiation. Soon after irradiation, the animals show a decrease in leukocyte concentration which reaches its nadir of approximately 10^3 cells per ml by day 20. Recovery commences thereafter and normal values are observed about 35 days postirradiation. A similar leukopenia is observed in dogs subjected to combined traumas of sublethal irradiation and abdominal gun shot wounds. Although the graph in figure 29 indicates a moderate leukocytosis by day 2 postirradiation, the subsequent decrease is probably more severe than that for radiation alone and persists beyond day 20. Recovery is not observed until day 50 postirradiation (Ref. 54). The highly elevated leukocytosis in wounded unirradiated dogs indicates the mobilization of white cells in the defense against infection. The decrease of leukocytes several days postirradiation is of course caused by the destruction of stem and precursor cells by the ionizing radiation. This is even further exacerbated after combined injuries.



Data from reference 54 (1958)

Figure 29. Effect of abdominal bullet wounds and sublethal irradiation on peripheral leukocyte concentration in dogs.

Chromov (Ref. 33) observed similar effects of white cell responses in rabbits subjected to 700-800 R of X-rays in combination with skin wounds. Sokolov (Ref. 138) demonstrated a decreased time of survival for wounded guinea pigs also subjected to ionizing radiation. The average survival time for irradiated guinea pigs was 12 days while that of animals subjected to combined traumas was 9.4 days.

Although the combination of two or more traumas often increases the injurious effects synergistically, two traumas do not necessarily always react that way (Ref. 33). If one of the traumas is much weaker, one observes at best an additive effect. Indeed, if wounding or burns occur at specific times prior to irradiation, a greatly decreased effect may be seen. However, mostly one observes synergistic increases of injury for animals subjected to two or more traumas.

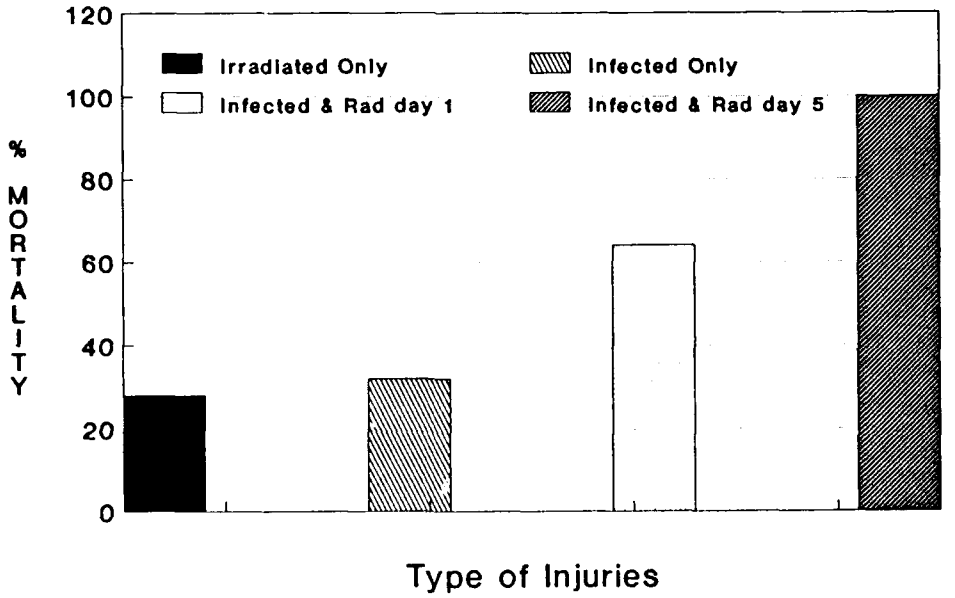
For example, combined radiation injuries often reduce the latent period of the radiation syndrome, and the manifest illness phase occurs much sooner. Rudenko (Ref. 122) demonstrated that the acute symptoms of radiation in rabbits occur between days 7 and 10 postirradiation. When the rabbits were also subjected to the mechanical trauma of a broken jaw, the manifest illness phase of radiation was observed between days 3 and 4, and the acute syndrome was much more severe. Filatov (Ref. 48) reported that dogs that apparently completely recovered from the effects of ionizing radiation, showed many of the symptoms of radiation disease when subsequently subjected to mechanical trauma.

In general, mortality is one and a half to three times greater in rats and rabbits subjected to combined traumas of mechanical injuries and radiation than in animals that are irradiated only (Refs. 17, 18, 33, 83).

Combined injuries increase mortality primarily due mostly to infection. A similar relationship is observed when animals are subjected to combined radiation and thermal injuries. Japanese who received both radiation and burns showed a greatly increased mortality (Ref. 134). The combining of radiation with wounds or burns is an additional burden that aggravates the effects of ionizing radiation and facilitates fatal infections. In turn of course, radiation delays proper healing of the other traumas. These facts were determined in a great number of experiments and clinical observations (Refs. 2, 4, 17-19, 24, 36, 48, 56, 70-72, 83, 85, 91, 95, 110, 112, 113, 118, 119, 134, 148, 150, 167).

The above cited reports clearly indicate that the traumatized animals become infected and that ionizing radiation reduces the systemic and local resistance to invading organisms. This is caused by a number of factors: the appearance of toxemia, leukopenia, reduced activity of the bone marrow and of the lymphatic system, reduced phagocytic activity of leukocytes, lowering of the immunological protective mechanisms, reduction of the barrier capabilities of tissues, increased permeability, decreased antitoxic function of a number of organs and tissues, decreased capability to counteract infection, etc. These conditions result in greater acceptance

of pathogens and microbes and their toxins by the irradiated animals as demonstrated in research by Russian and American experimenters (Refs. 23, 50, 58, 66, 105, 106, 125, 139, 152). In other words, the sensitivity to staphylococci, streptococci, anerobic bacteria, and many other pathogens becomes much greater. This sensitivity increases further with increasing radiation exposure. Infectious complications play an important role in irradiated animals and clearly this role is greatly enhanced after combined radiation injuries. Figure 30 depicts the increase in mortality for combined injury (infection plus irradiation) over that observed for radiation only or infection only. Furthermore, if the infection occurs immediately after irradiation, it is increased from about 30 pct to 64 pct; and if it occurs 5 days later, the mortality is 100 pct (Ref. 33).



Data from reference 33 (1964)

Figure 30. Effect on mortality of infecting irradiated mice with anaerobic bacteria immediately and 5 days postirradiation.

Table 4, representing the results from an experiment by G.T. Golikov (Ref. 52), shows the high mortality in irradiated and nonirradiated animals with infected wounds and the significant reduction in mortalities after treatment with specific antibiotics.

Table 4. Frequency of wound infections and mortalities in treated and untreated animals (G. T. Golikov, Ref. 52).

	Number Animals	Irradiated No	Irradiated Yes	Infected	Deaths	Mortality
A. No Treatment	8	8	0	7	7	88
	8	0	8	6	5	63
B. Treatment						
Penicillin + Bicillin	15	0	15	8	2	13
Bicillin	4	0	4	1	0	0
Biomycin	19	0	19	7	13	68

Infection is further favored in combined injuries since wounds are not a good barrier against bacteria. This is not only true for exogenous but also for endogenous infections through radiation-injured intestines. This process of autoinfection complicates the recovery from the radiation damage, shortens the remaining life, and increases the number of lethalities.

Intensive development of a microflora occurs in the blood circulation in the second week after irradiation. The continuous bacteremia is the cause for lethality. Autopsies of Japanese casualties often revealed the presence of a bacteremia (Ref. 33). Bacteriological tests of the blood of irradiated animals revealed Enteritis and Paraenteritic bacteria (55 pct), Enterococci (27 pct), Staphylo and Streptococci (11 pct), Anerobic bacteria (3 pct), Proteus (2 pct) and Pyocyanobacteria (2 pct). Infections shorten the latent period in rodents, and manifest clinical symptoms appear 3-4 days rather than 9-10 days after irradiation (Refs. 52, 58). Furthermore, infections in irradiated or combined injury animals always delay recovery (Ref. 33).

The natural protective ability of properdins to kill bacteria, neutralize viri, and lyze abnormal erythrocytes is an important part of the body's protective mechanisms, and in irradiated animals as well as in those that suffer hemorrhage or are in shock, the concentration of properdins is greatly reduced two weeks after trauma (Ref. 107). Chromov et al. (Ref. 33) measured the concentration of properdins in the blood of rats exposed to 500 R X-rays and found a significant decrease within a few days after irradiation. Similar results were obtained from rats with wounds contaminated with radioiodine and radiophosphorus (figure 17).

In animals with combined radiation injuries, suppurative infections such as abscesses, erysipelas, phlegm, pneumonia, sepsis and other complications caused by anaerobic bacteria, are increased (Refs. 24, 34, 38, 117). Studying several animal species after irradiation, Sosova (Ref. 139) determined the following general course of events from the local process of infection:

1. The infection proceeds with hemorrhage and necrosis.

2. Irradiated animals have a diminished capability for reducing the propagation of microbes. Thus the number of microbes observed in wounds of postirradiated animals is increased by a factor of 10^3 to 10^6 when compared with that of nonirradiated animals.

3. After irradiation, the capacity for localization of infections is greatly decreased. Therefore, most infections become systemic and develop into a bacteremia.

Bacterial infections have been shown to be lethal complications of neutropenia in several studies. Furthermore antibiotics alone are often inadequate to combat these infections. Recent promising discoveries indicate that as long as sufficient pluripotential stem cells survive, treatment with granulocyte-macrophage colony stimulating factor (GM-CSF) or multi-CSF (Interleukin 3) enhances granulocyte production (Ref. 149). The combination of antibiotics and granulocyte colony-stimulating factor are seen to greatly increase survival after combined radiation injuries.

Researchers at the Armed Forces Radiobiology Research Institute (AFRRI) using the bacterial cell wall derivative glycolipid trehalose dimycolate (TDM) derived from Mycobacterium phlei or a synthetic preparation TDM were able to enhance survival significantly in irradiated mice (Ref. 84). TDM injected 1 hour after sublethal irradiation increased resistance to a lethal Klebsiella pneumoniae challenge 4 or 14 days later. Tests will be conducted to measure the effectiveness of TDM in animals subjected to combined radiation injuries.

SECTION 6

CONCLUSION

The systemic response to combined injury depends on the magnitude and timing of the component traumas. If the traumas independently cause about the same level of injury or mortality, i.e., if they are of the same "magnitude", then each will contribute equally towards the combined injury. If they differ in magnitude, two alternative outcomes are possible:

1. If the smaller trauma hits first, it is possible that the organism will respond by temporarily increasing its resistance to trauma. A case in point is the effect of wounds or burns that also involve moderate bleeding to stimulate increased hematopoiesis in the bone marrow. The hyperactive bone marrow responds better to moderate radiation exposure and affords the organism better protection. The net effect is a less severe injury or fewer fatalities.

2. If the larger trauma hits first, or both occur simultaneously, the combined effect will be additive or strongly synergistic depending on the magnitude and timing of the components. The result is a more severe injury or an increased number of fatalities.

Four main types of combined injuries resulting from detonation of a nuclear weapon have been described:

1. Thermal trauma and irradiation
2. Primary, secondary, and tertiary blast effects and irradiation
3. Blast and thermal trauma
4. Thermal and mechanical trauma and irradiation

Finally, the characteristics of combined injury are as follows:

1. Radiation effects may be ameliorated by prior exposure to other sublethal stresses or by subsequent treatment with stimulators of hematopoiesis and/or treatment with antibiotics.

2. Sublethal levels of radiation combined with low intensity stresses of burns or wounds may interact to cause a moderate number of fatalities by decreasing immune defenses and permitting entry of opportunistic bacteria.

3. Increasing injury to the blood forming system may further compromise immune defenses and result in synergistic augmentation of the numbers of fatalities. For example, an LD10 from X-irradiation may become 100% lethal in combination with sublethal wounds or burns.

4. Decreased reaction capability of organisms, i.e., absence of leukocytosis and fever in pyogenic infections.

5. Impaired wound healing and delayed consolidation of fractures.

6. Increased tendency to develop circulatory failure and shock after only moderate blood volume loss.

7. Increased susceptibility to complicating infections.

It has been postulated that response to trauma can be divided into two types, local and systemic. A local response is usually independent of the type of harmful influence since it is primarily governed by the capability of cells to react to injury. The systemic response is complex and depends on humoral and cellular involvement of pituitary-adrenal and reticuloendothelial systems (Ref. 53). However, the ways in which the body

responds to traumas are limited, and a basic pattern in responses emerges (Ref. 126).

Simultaneous exposure to burn or blast injuries and ionizing radiation appears to induce hypovolemic conditions that may lead to shock (Ref. 67). Radiation increases the sensitivity to shock (Ref. 86). However, shock, which occurs primarily during the first three days postirradiation, is caused by the burn or blast injuries in sublethally irradiated animals. Wounds present a portal of entry for opportunistic bacteria, and subsequent to the first three days, it is infection in the radiation-induced immune-compromised host that induces incapacitation and mortality. Depending on the size of the wound or burn and the dose of radiation, performance in untreated personnel may become degraded within hours due to shock or certainly within days due to infection.

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APPENDIX A

GLOSSARY OF TERMS

ADDITIVE EFFECT. The summation of the effects of two or more drugs or treatments which produce the same kind of effect when administered in combination.

ANAEROBIC. Growing or living in the absence of molecular oxygen.

ANTAGONISM. Opposing action of a drug or treatment against another one usually resulting in a decreased effect.

BACTEREMIA. The presence of bacteria in the blood.

COMBINED INJURY. A complex injury caused by exposure to two or more forms of energy or traumata of various kinds. For military purposes radiation is considered one of the traumata and simultaneous exposure is usually assumed.

DYSTROPHY. Any disorder arising from defective or faulty nutrition.

EMBOLISM. The sudden blocking of an artery by a clot or foreign material which has been brought to its site by the blood current.

ENDOTOXIN. A heat-stable toxin present in the bacterial cell but not in cell force filtrates of cultures of intact bacteria. They are found primarily in gram-negative organisms.

FERRITIN. Composed of apoferritin and ferric oxide. This is one of the chief forms in which iron is stored in the body.

GM-CSF. Granulocyte-macrophage colony stimulating factor.

GRANULOCYTES. White blood cells containing neutrophil, basophil or eosinophil granules in the cytoplasm.

GRAY (Gy). Unit of radiation absorbed dose for any radiation type and in any material. 1 Gy = 1J/Kg = 100 rad.

HEMATOPOIESIS. Process of formation of blood cells.

HEMATOPOIETIC SYSTEM. The tissues concerned in production of the blood, including bone marrow and lymphatic tissue.

HEMORRHAGE. The escape of blood from the vessels; bleeding.

HUMOR. A fluid or semifluid substance used in anatomical nomenclature to designate certain fluid materials in the body.

HUMORAL. Pertaining to the humors of the body.

HUMORAL FACTOR. A chemical substance which leaves the cell that produced it and can act at a distance, travelling to the target cells via the blood.

HYPOTONIC. Denotes a solution which, when bathing a cell, causes a net flow of water across the semipermeable cell membrane into the cell.

HYPOVOLEMIC. Abnormally decreased volume of circulating fluid or plasma in the body.

KVP. Kilo Volt peak; kilovolt is a unit of electromotive force equal to 1000 volts.

LEUKOCYTOSIS. A transient increase in the number of leukocytes in the blood.

LEUKOPENIA. Reduction of the number of leukocytes in the blood.

LD 20/3. Lethal dose of 20 percent of an irradiated population group by the 3rd day post-irradiation.

LYMPHOCYTE. A mononuclear leukocyte 7mu to 20mu in diameter. It is chiefly a product of lymphoid tissue and participates in humoral and cell-mediated immunity.

MACROPHAGE. Highly phagocytic cells derived from monocytes, with a small, oval, sometimes indented nucleus.

NADIR. The lowest point on a curve.

NECROTIC TISSUE. Death tissue.

NOBLE-COLLIP DRUM. A drum which rotates at 40 rpm. Small animals are placed into the drum for approximately 650 turns. Animals are carried upwards with each revolution and then fall, thereby receiving widespread body trauma.

NONHEMOLYTIC. Not caused by hemolysis, which refers to the separation of hemoglobin from red cells and its appearance in the plasma.

PHAGOCYTIC ACTIVITY. Refers to the activity of cells which have the capability to ingest microorganisms or other cells and foreign particles. Such cells are called phagocytes.

PHAGOCYTE. Cells that ingest microorganism or other cells and foreign particles (i.e. neutrophilic leukocytes).

PHLEBOTOMY. Incision of a vein, as for letting of blood.

PRODROMAL. Indicating the onset of disease or morbid state.

PROPERDINS. A relatively heat-labile, normal serum protein that, in the presence of complement component C3 and magnesium ions, acts nonspecifically against gram-negative bacteria and viruses.

PYOGENIC INFECTION. An infection caused by pus-producing organisms.

ROENTGEN (R). A unit of exposure dose in air that applies only to X- and gamma rays. When air at STP is exposed to 1.0R of radiation, 2.08×10^9 ion pairs are created per cm^3.

RAD. Unit of radiation absorbed dose for any radiation type and in any material. 1 rad = 100 ergs/g = 0.01 Gy

RADIOSENSITIVE. The sensitivity of cells and tissues to ionizing radiation is in direct proportion to their reproductive activity and inversely proportional to their degree of differentiation.

RETICULOENDOTHELIAL. Pertaining to tissues having both reticular and endothelial attributes.

SEPTICEMIA. Systemic disease associated with the presence and persistence of pathogenic microorganisms or their toxins in the blood.

SYNERGISM. Cooperative action of discrete agents such that the total effect is greater than the sum of the effects taken independently.

TREHALOSE DIMYCOLATE (TDM). An immunomodulator derived from the cell wall of Microbacterium phLei.

TRAUMA (pl. TRAUMATA). A physical or psychic wound or injury.

APPENDIX B

DATA LISTING

Table 5. Summary of animal data used in figures 1 to 30.

Burn Stress Before Radiation

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
Baker & Valeriote	8(1966)	Albino	250KvP Xray (R)	1min IR Burn %	Days							
		M/Rat	700	16	-4		22	GI/Shock	0-5	Syner	None	N/A
		M/Rat	700	16	-4	*10	90	BM/Infect	6-8	Syner	None	N/A
		M/Rat	700	16	-4		100	BM/Infect	9-30	Syner	None	N/A
		M/Rat	700	16	-3		100	GI/Shock	0-5	Syner	None	N/A
		M/Rat	700	16	-3	*10	100	BM/Infect	6-8	Syner	None	N/A
		M/Rat	700	16	-3		100	BM/Infect	9-30	Syner	None	N/A
		M/Rat	700	16	-1		12	GI/Shock	0-5	Syner	None	N/A
		M/Rat	700	16	-1	*10	62	BM/Infect	6-8	Syner	None	N/A
		M/Rat	700	16	-1		80	BM/Infect	9-30	Syner	None	N/A
		M/Rat	700	16	-.25		0	None	N/A		None	N/A
		M/Rat	700	16	-.25	*10	50	BM/Infect	6-8	Syner	None	N/A
		M/Rat	700	16	-.25		100	BM/Infect	9-30	Syner	None	N/A
Schildt	127(1972)	CBA	260KvP Xray	Scald Burn	Days							
		M/Mouse	Rs	B10	-2	20	0	None	N/A	N/A	None	N/A
		M/Mouse	Rs	B10	-4	20	10	Shock	0-5	Burn	None	N/A
		M/Mouse	Rs	B10	-6	20	5	Shock	0-5	Burn	None	N/A
		M/Mouse	Rs	B10	-8	20	5	Shock	0-5	Burn	None	N/A
		M/Mouse	Rs	B10	-12	20	0	None	N/A	N/A	None	N/A
		M/Mouse	R10	Bs	-1	20	25	Shock	0-5	Syner	None	N/A
		M/Mouse	R10	Bs	-3	20	20	Shock	0-5	Syner	None	N/A
		M/Mouse	R10	Bs	-5	20	65	Shock	0-5	Syner	None	N/A
		M/Mouse	R10	Bs	-8	20	45	Shock	0-5	Syner	None	N/A
		M/Mouse	R10	Bs	-12	20	40	BM/Infect	0-12	Syner	None	N/A

*Group of 10 rats observed at 3 times post irradiation

Table 5. Summary of animal data used in figures 1 to 30. (continued)

Concurrent Exposure to Radiation and Burn

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
Alpen & Sheline	5(1954)	S-D	250KvP Xray (R)	Scald Burn	Days							
		F/Rat	0	24%	0	9	11	Shock	0-2		None	N/A
		F/Rat	0	33%	0	28	43	Shock	0-2		None	N/A
		F/Rat	0	37%	0	2	100	Shock	0-2		None	N/A
		F/Rat	0	33%	0	28	7	BM/Infect	3-30		None	N/A
		F/Rat	100	24%	0	3	0	None	0-2	Antag	None	N/A
		F/Rat	100	33%	0	11	54	Shock	0-2	Syner	None	N/A
		F/Rat	100	35%	0	10	70	Shock	0-2	Burn	None	N/A
		F/Rat	100	33%	0	10	10	BM/Infect	3-30	Syner	None	N/A
		F/Rat	250	24%	0	7	43	Shock	0-2	Syner	None	N/A
		F/Rat	250	33%	0	14	65	Shock	0-2	Syner	None	N/A
		F/Rat	250	35%	0	13	92	Shock	0-2	Burn	None	N/A
		F/Rat	250	24%	0	3	33	BM/Infect	3-30	Syner	None	N/A
		F/Rat	250	33%	0	7	86	BM/Infect	3-30	Syner	None	N/A
		F/Rat	500	24%	0	16	40	Shock	0-2	Syner	None	N/A
		F/Rat	500	27%	0	7	70	Shock	0-2	Syner	None	N/A
		F/Rat	500	9%	0	28	50	BM/Infect	3-30	Syner	None	N/A
		F/Rat	500	16%	0	22	73	BM/Infect	3-30	Syner	None	N/A
		F/Rat	500	26%	0	1	100	BM/Infect	3-30	Syner	None	N/A
Valeriote & Baker	159(1964)	Albino	250KvP Xray (R)	1min IR Burn %	Days							
		M/Rat	550	0	0	10 to 26	0	None	N/A		None	N/A
		M/Rat	650	0	0	10 to 26	4	GI/Shock	0-5		None	N/A
		M/Rat	700	0	0	10 to 26	0	None	N/A		None	N/A
		M/Rat	750	0	0	10 to 26	7	GI/Shock	0-5		None	N/A
		M/Rat	550	0	0	10 to 26	4	BM/Infect	6-8		None	N/A
		M/Rat	650	0	0	10 to 26	6	BM/Infect	6-8		None	N/A
		M/Rat	700	0	0	10 to 26	6	BM/Infect	6-8		None	N/A
		M/Rat	750	0	0	10 to 26	55	BM/Infect	6-8		None	N/A
		M/Rat	550	0	0	10 to 26	20	BM/Infect	9-30		None	N/A

Table 5. Summary of animal data used in figures 1 to 30. (continued)

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
Valeriote & Baker (cont.)	159(1964)	Albino	250KvP Xray (R)	1min IR Burn %	Days							
		M/Rat	650	0	0	10 to 26	29	BM/Infect	9-30		None	N/A
		M/Rat	700	0	0	10 to 26	39	BM/Infect	9-30		None	N/A
		M/Rat	750	0	0	10 to 26	80	BM/Infect	9-30		None	N/A
		M/Rat	550	16	0	10 to 26	0	None	N/A		None	N/A
		M/Rat	650	16	0	10 to 26	0	None	N/A		None	N/A
		M/Rat	700	16	0	10 to 26	15	GI/Shock	0-5	Syner	None	N/A
		M/Rat	750	16	0	10 to 26	20	GI/Shock	0-5	Syner	None	N/A
		M/Rat	550	16	0	10 to 26	20	BM/Infect	6-8	Syner	None	N/A
		M/Rat	650	16	0	10 to 26	16	BM/Infect	6-8	Syner	None	N/A
		M/Rat	700	16	0	10 to 26	55	BM/Infect	6-8	Syner	None	N/A
		M/Rat	750	16	0	10 to 26	60	BM/Infect	6-8	Additive	None	N/A
		M/Rat	550	16	0	10 to 26	50	BM/Infect	9-30	Syner	None	N/A
		M/Rat	650	16	0	10 to 26	40	BM/Infect	9-30	Syner	None	N/A
		M/Rat	700	16	0	10 to 26	85	BM/Infect	9-30	Syner	None	N/A
		M/Rat	750	16	0	10 to 26	90	BM/Infect	9-30	Additive	None	N/A
				1.5 min IR								
		M/Rat	550	16	0	10 to 26	20	GI/Shock	0-5	Syner	None	N/A
		M/Rat	650	16	0	10 to 26	10	GI/Shock	0-5	Syner	None	N/A
		M/Rat	700	16	0	10 to 26	20	GI/Shock	0-5	Syner	None	N/A
		M/Rat	750	16	0	10 to 26	40	GI/Shock	0-5	Syner	None	N/A
		M/Rat	550	16	0	10 to 26	20	BM/Infect	6-8	Syner	None	N/A
		M/Rat	650	16	0	10 to 26	35	BM/Infect	6-8	Syner	None	N/A
		M/Rat	700	16	0	10 to 26	70	BM/Infect	6-8	Syner	None	N/A
		M/Rat	750	16	0	10 to 26	80	BM/Infect	6-8	Syner	None	N/A
		M/Rat	550	16	0	10 to 26	40	BM/Infect	9-30	Syner	None	N/A
		M/Rat	650	16	0	10 to 26	66	BM/Infect	9-30	Syner	None	N/A
		M/Rat	700	16	0	10 to 26	90	BM/Infect	9-30	Syner	None	N/A
		M/Rat	750	16	0	10 to 26	100	BM/Infect	9-30	Syner	None	N/A

Table 5. Summary of animal data used in figures 1 to 30. (continued)

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
Baker & Valeriote	8(1966)	Albino	250KvP X Xray (R)	1min IR Burn %	Days							
		M/Rat	700	0	0	10	0	None	0-5		None	N/A
		M/Rat	700	0	0	10	18	BM/Infect	6-8		None	N/A
		M/Rat	700	0	0	10	40	BM/Infect	9-21		None	N/A
		M/Rat	700	0	0	10	40	BM/Infect	22-30		None	N/A
		M/Rat	700	16	0	10	17	BM/Infect	0-5	Syner	None	N/A
		M/Rat	700	16	0	10	58	BM/Infect	6-8	Syner	None	N/A
		M/Rat	700	16	0	10	90	BM/Infect	9-21	Syner	None	N/A
		M/Rat	700	16	0	10	90	BM/Infect	22-30	Syner	None	N/A
Schildt	127(1972)	CBA	260KvP Xray	Scald Burn	Days							
		M/Mouse	0	Bs	0	20	0	None	N/A		None	N/A
		M/Mouse	0	B10	0	20	5	Shock	0-3		None	N/A
		M/Mouse	Rs	0	0	20	0	None	N/A		None	N/A
		M/Mouse	R10	0	0	20	15	BM/Infect	4-12		None	N/A
		M/Mouse	Rs	B10	0	20	20	Shock	0-3	Syner	None	N/A
		M/Mouse	Rs	B10	0	20	20	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	B10	0	20	95	Shock	0-3	Syner	None	N/A
		M/Mouse	Rs	Bs	0	20	15	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	Bs	0	20	45	Shock	0-3	Syner	None	N/A
Brooks	26(1952)	Mongrel	1000KvP Xray (R)	Contact Burn %	Days							
		Dog	0	20	0	40	12	Infect	5-14		None	N/A
		Dog	100	0	0	10	0	N/A	N/A		None	N/A
		Dog	25	20	0	25	20	BM/Infect	5-14	Syner	None	N/A
		Dog	100	20	0	40	73	BM/Infect	8-14	Syner	None	N/A
		Dog	100	20	0	28	14	BM/Infect	8-14	Antag	Penici	Reduce 60%
Baxter	13(1953)	Yorkshire Pig	220KvP Xray (R)	Flash Burn %	Days							
		Pig	0	10-15	0	10	0	N/A	N/A		None	N/A
		Pig	400	0	0	10	20	Infect	6-30		None	N/A
		Pig	400	10-15	0	10	90	Infect	6-30	Syner	None	N/A
		Pig	400	10-15	0	10	20	Infect	6-30	Antag	Streptomy	Reduce 70%

Table 5. Summary of animal data used in figures 1 to 30. (continued)

Burn Stress After Irradiation

AUTHORS	REF(YP'	STRESS ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	MORTALITY PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	CAUSE	COMBINED SURVIVAL DAYS	ANTIBIOTIC INJURY EFFECT	ANTIBIOTIC TYPE	EFFECT % REDUCT
Baker & Valeriote	8(1966)	Albino	250KvP Xray (R)	1min IR Burn %	Days							
		M/Rat	700	16	1		0	None	N/A	Antag	None	N/A
		M/Rat	700	16	1	*10	90	BM/Infect	9-30	Syner	None	N/A
		M/Rat	700	16	1		10	BM/Infect	6-8	Antag	None	N/A
		M/Rat	700	16	3		0	None	N/A	Syner	None	N/A
		M/Rat	700	16	3	*10	50	BM/Infect	6-8	Syner	None	N/A
		M/Rat	700	16	3		100	BM/Infect	9-30	Syner	None	N/A
		M/Rat	700	16	4		0	None	N/A	Syner	None	N/A
		M/Rat	700	16	4	*10	12	BM/Infect	6-8	Antag	None	N/A
		M/Rat	700	16	4		80	BM/Infect	9-30	Syner	None	N/A
		M/Rat	700	16	1.29		36	BM/Infect	6-8	Syner	None	N/A
		M/Rat	700	16	1.29	*10	0	None	N/A	Antag	None	N/A
		M/Rat	700	16	1.29		80	BM/Infect	9-30	Syner	None	N/A
Schildt	127(1972)	CBA	260KvP Xray	Scald Burn	Days							
		M/Mouse	Rs	B10	2	20	5	Shock	0-3		None	N/A
		M/Mouse	Rs	B10	4	20	10	Shock	0-3		None	N/A
		M/Mouse	Rs	B10	8	20	5	Shock	0-3		None	N/A
		M/Mouse	Rs	B10	12	20	15	BM/Infect	0-30	Syner	None	N/A
		M/Mouse	Rs	B10	20	20	0	None	0-30	Antag	None	N/A
		M/Mouse	R10	Bs	2	20	75	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	Bs	4	20	90	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	Bs	8	20	95	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	Bs	12	20	100	Infect	0-30	Syner	None	N/A
		M/Mouse	R10	Bs	20	20	70	Infect	0-30	Syner	None	N/A
		M/Mouse	R10	Bs	30	20	53	Infect	0-30	Syner	None	N/A

*Group of 10 rats observed at 3 times post irradiation

Table 5. Summary of animal data used in figures 1 to 30. (continued)

Blast or Mechanical Injury Before Irradiation

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
Koslowski & Messerschmidt	68(1968)		250KvP Xray (R)	Skin Wounds	Days							
		M/Mouse	510	LD6	-8	>100	5	BM/Infect	0-30	Antag	None	N/A
		M/Mouse	510	LD6	-4	>100	26	BM/Infect	0-30	Rad	None	N/A
		M/Mouse	510	LD6	-2	>100	40	BM/Infect	0-30	Additive	None	N/A
Stromberg	145(1968)	W.R.	^{60}CO (R)		Days							
		M/Rat	875	Wounds	-4	18	44	BM/Infect	0-30	Rad	None	N/A
		M/Rat	875	Wounds	-1	18	22	BM/Infect	0-30	Antag	None	N/A
Ledney	75(1985)	BCBF1	^{60}CO (Gy)		Days							
		F/Mouse	9	Wound	-7	16	100	BM/Infect	0-30	Rad	None	N/A
		F/Mouse	9	Wound	-6	16	100	BM/Infect	0-30	Rad	None	N/A
		F/Mouse	9	Wound	-5	16	100	BM/Infect	0-30	Rad	None	N/A
		F/Mouse	9	Wound	-4	16	100	BM/Infect	0-30	Rad	None	N/A
		F/Mouse	9	Wound	-3	16	95	BM/Infect	0-30	Rad	None	N/A
		F/Mouse	9	Wound	-2	16	50	BM/Infect	0-30	Antag	None	N/A
		F/Mouse	9	Wound	-1	16	10	BM/Infect	0-30	Antag	None	N/A
Schmidt	127(1972)		260KvP Xray	Mech Drum	Days							
		CBA M/Mouse	R10	Ms	-1	20	15	BM/Infect	0-30	Syner	None	N/A
		M/Mouse	R10	Ms	-3	20	30	BM/Infect	0-30	Syner	None	N/A
		M/Mouse	R10	Ms	-5	20	55	BM/Infect	0-30	Syner	None	N/A
		M/Mouse	R10	Ms	-8	20	25	BM/Infect	0-30	Syner	None	N/A
		M/Mouse	R10	Ms	-12	20	5	BM/Infect	0-30	Antag	None	N/A
		M/Mouse	Rs	M10	-1	20	5	BM/Infect	0-30	Antag	None	N/A
		M/Mouse	Rs	M10	-3	20	5	BM/Infect	0-30	Antag	None	N/A
		M/Mouse	Rs	M10	-5	20	5	BM/Infect	0-30	Antag	None	N/A
		M/Mouse	Rs	M10	-8	20	10	BM/Infect	0-30	Mech	None	N/A
		M/Mouse	Rs	M10	-12	20	10	BM/Infect	0-30	Mech	None	N/A

Table 5. Summary of animal data used in figures 1 to 30. (continued)

Concurrent Exposure to Blast/Mechanical Injury and Radiation

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
Richmond	115(1968)	S-D	250KvP Xray(Gy)	Blast psi	Days							
		U/Rat	0	26	N/A	40	5	Shock	0-1		None	N/A
		U/Rat	6.0	0	N/A	80	46	Infect	6-30		None	N/A
		U/Rat	6.0	26	0	80	52	Shock Infect	0-1 8% 2-30 44%	Additive	None	N/A
Koslowski & Messerschmidt	68(1968)		250 KvP Xray (R)	Wound	Days							
		U/Mouse	510	0	N/A	>100	26	Infect	0-30		None	N/A
		U/Mouse	0	LD10	N/A	>100	10	Shock	0-5		None	N/A
		U/Mouse	510	LD10	-.05	>100	42	Shock	0-5	Additive	None	N/A
		U/Mouse	510	LD10	+.05	>100	60	Shock	0-5	Syner	None	N/A
Stromberg	145(1968)	W.R.	^{60}CO (R)	Skin Wound	Days							
		M/Rat	875	0	N/A	18	44	BM/Infect	0-30	Rad	None	N/A
		M/Rat	0	LS	N/A	18	0	None	N/A		None	N/A
Ledney	79(1985)		^{60}CO (Gy)		Days							
		F/Mouse	9	Wound	0	16	5	BM/Infect	0-30	Antag	None	N/A
		F/Mouse	9	Wound	0	16	60	BM/Infect	0-30	Antag	None	N/A
Schildt	127(1972)	CBA	260KvP Xray	Mech Drum	Days							
		M/Mouse	Rs	0	N/A	20	0	None	N/A		None	N/A
		M/Mouse	R10	0	N/A	20	5	BM/Infect	0-30		None	N/A
		M/Mouse	0	Ms	N/A	20	0	None	N/A		None	N/A
		M/Mouse	0	M10	N/A	20	15	Shock	0-3		None	N/A
		M/Mouse	Rs	M10	0	20	20	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	Ms	0	20	10	Shock	0-3	Additive	None	N/A
		M/Mouse	Rs	Ms	0	20	0	None	N/A		None	N/A
		M/Mouse	R10	M10	0	20	25	Shock	0-3	Syner	None	N/A

Table 5. Summary of animal data used in figures 1 to 30. (continued)

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
Jones	63(1971)		N-gamma Rad	Blast psi	Days							
		U/Sheep	0	0	N/A	8	0	N/A	N/A		None	N/A
		U/Sheep	422	0	0	8	0	N/A	N/A		None	N/A
		U/Sheep	0	145	0	8	25	Infect	30-35		None	N/A
		U/Sheep	412	138	0	8	50	Lung	6-25		None	N/A
McKenna & Zweifach	86(1957)	Carworth	200KvP Xray (R)	Mech Drum	Days							
		U/Rat	0	LD55	N/A	10	55	Shock	0-5	Drum	None	N/A
		U/Rat	350	0	N/A	10	0	None	N/A		None	N/A
		U/Rat	650	0	N/A	10	50	BM/Infect	0-30	Rad	None	N/A
		U/Rat	900	0	N/A	10	100	BM/Infect	0-30	Rad	None	N/A

Blast or Mechanical Injury After Irradiation

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
Jones	63(1971)	Sheep	N-gamma Rad	Blast psi	Days							
		U/Sheep	422	133	7	8	25	BM/Infect	9-60	Additive	None	N/A
		U/Sheep	434	136	14	8	62	BM/Infect	14-60	Syner	None	N/A
		U/Sheep	407	146	21	8	25	BM/Infect	18-60	Antag	None	N/A
		U/Sheep	445	146	28	8	38	BM/Infect	19-60	Antag	None	N/A
Richmond	115(1968)	S-D	250KvP Xray(Gy)	Blast psi	Days							
		U/Rat	6.0	26	7	79	82	Shock	0-1 20%	Syner	None	N/A
								Infect	2-30 60%			
Koslowski & Messerschmidt	68(1968)	Mouse	250KvP Xray (R)	Skin Wound	Days							
		U/Mouse	510	LD10	2	>100	75	Shock	0-5	Syner	None	N/A
		U/Mouse	510	LD10	4	>100	68	Shock	0-	Syner	None	N/A
		U/Mouse	510	LD10	6	>100	41	BM/Infect	6-30	Syner	None	N/A
		U/Mouse	510	LD10	7	>100	50	BM/Infect	6-30	Syner	None	N/A
		U/Mouse	510	LD10	8	>100	74	BM/Infect	6-30	Syner	None	N/A
		U/Mouse	510	LD10	10	>100	70	BM/Infect	6-30	Syner	None	N/A
		U/Mouse	510	LD10	15	>100	10	BM/Infect	6-30	Antag	None	N/A

Table 5. Summary of animal data used in figures 1 to 30. (continued)

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
Stromberg & Messerschmidt	145(1968)	W.R. Rats	250KvP Xray (R)		Days							
		M/Rat	875	Wound	1	18	44	BM/Infect	0-30	Rad	None	N/A
		M/Rat	875	Wound	4	18	78	BM/Infect	0-30	Syner	None	N/A
Ledney	75(1985)		^{60}CO (Gy)		Days							
		F/Mouse	9	Wound	1	16	80		0-30	Antag	None	N/A
		F/Mouse	9	Wound	2	16	100		0-30	Rad	None	N/A
Schildt	127(1972)	CBA	260KvP Xray	Mech Drum	Days							
		M/Mouse	Rs	M10	2	20	15	Shock	0-3	Syner	None	N/A
		M/Mouse	Rs	M10	4	20	20	Shock	0-3	Syner	None	N/A
		M/Mouse	Rs	M10	8	20	20	Shock	0-3	Syner	None	N/A
		M/Mouse	Rs	M10	12	20	10	Shock	0-3	Additive	None	N/A
		M/Mouse	Rs	M10	20	20	5	Shock	0-3	Antag	None	N/A
		M/Mouse	Rs	M10	30	20	10	Shock	0-3	Additive	None	N/A
		M/Mouse	R10	Ms	2	20	30	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	Ms	4	20	75	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	Ms	8	20	95	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	Ms	12	20	90	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	Ms	20	20	70	Shock	0-3	Syner	None	N/A
		M/Mouse	R10	Ms	30	20	10	Shock	0-3	Drum	None	N/A
McKenna & Zweifach	86(1957)	Carworth	200KvP Xray (R)	Mech Drum	Days							
		U/Rat	550	LD55	4	10	90	Shock	0-5	Syner	None	N/A
		U/Rat	550	LD55	7	10	86	Shock	0-5	Syner	None	N/A
		U/Rat	550	LD55	14	10	75	Shock	0-5	Syner	None	N/A
		U/Rat	550	LD55	26	10	75	Shock	0-5	Syner	None	N/A
		U/Rat	550	LD55	21	10	35	BM/Infect	0-30	Antag	None	N/A
		U/Rat	550	LD55	30	10	40	BM/Infect	0-30	Antag	None	N/A
		U/Rat	350	LD55	7	10	75	Shock	0-5	Syner	None	N/A
		U/Rat	350	LD55	14	10	25	BM/Infect	0-30	Antag	None	N/A
		U/Rat	350	LD55	21	10	33	BM/Infect	0-30	Antag	None	N/A
		U/Rat	650	LD55	1	10	43	BM/Infect	0-30	Antag	None	N/A

Table 5. Summary of animal data used in figures 1 to 30. (continued)

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
McKenna & Zweifach (cont.)	86(1957)	Carworth U/Rat	200KvP Xray (R) 650	Mech Drum LD55	Days 2	10	78	Shock	0-5	Syner	None	N/A
		U/Rat	650	LD55	3	10	86	Shock	0-5	Syner	None	N/A
		U/Rat	650	LD55	4	10	75	Shock	0-5	Syner	None	N/A
		U/Rat	650	LD55	5	10	87	Shock	0-5	Syner	None	N/A
		U/Rat	650	LD55	6	10	100	Shock	0-5	Syner	None	N/A
		U/Rat	650	LD55	30	10	100	Shock	0-5	Syner	None	N/A
		U/Rat	900	LD55	1	10	17	Shock	0-5	Antag	None	N/A
		U/Rat	900	LD55	2	10	80	Shock	0-5	Antag	None	N/A
		U/Rat	900	LD55	3	10	100	Shock	0-5	Rad	None	N/A
		U/Rat	900	LD55	4	10	77	Shock	0-5	Antag	None	N/A
		U/Rat	900	LD55	5	10	100	Shock	0-5	Rad	None	N/A
		U/Rat	900	LD55	30	10	100	Shock	0-5	Rad	None	N/A

Infection and Ionizing Radiation

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	STRESS PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
Schildt	130(1968)	CBA M/Mouse	260KvP Xray R50	Toxin Ts	Days -3	*	15	Toxin	0-30	Antag	None	N/A
		M/Mouse	R50	Ts	-1	*	60	Toxin	0-30	Additive	None	N/A
		M/Mouse	R50	Ts	0	*	90	Toxin	0-30	Syner	None	N/A
		M/Mouse	R10	Ts	0	*	70	Toxin	0-30	Syner	None	N/A
		M/Mouse	R10	Ts	2	*	71	Toxin	0-30	Syner	None	N/A
		M/Mouse	R10	Ts	4	*	85	Toxin	0-30	Syner	None	N/A
		M/Mouse	R10	Ts	6	*	96	Toxin	0-30	Syner	None	N/A
		M/Mouse	R10	Ts	8	*	90	Toxin	0-30	Syner	None	N/A
		M/Mouse	R10	Ts	10	*	68	Toxin	0-30	Syner	None	N/A
		M/Mouse	R10	Ts	14	*	40	Toxin	0-30	Syner	None	N/A
		M/Mouse	R10	Ts	28	*	15	Toxin	0-30	Additive	None	N/A
		M/Mouse	R10	Ts	35	*	8	Toxin	0-30	Additive	None	N/A

* Total = 1700 mice

Table 5. Summary of animal data used in figures 1 to 30. (continued)

Radiation and Skull/ Brain Injuries (Effects of Antibiotics)

AUTHORS	REF(YR)	ANIMAL SEX/TYPE	STRESS RADIATION	STRESS OTHER	PRE(-) POST(+)	MORTALITY NUMBER TESTED	MORTALITY PERCENT MORT	MORTALITY CAUSE	SURVIVAL DAYS	COMBINED INJURY EFFECT	ANTIBIOTIC TYPE	ANTIBIOTIC EFFECT % REDUCT
			170KvP Xray (R)		Days							
Alexandrov	3(1962)	U/Rabbit	600	0	0	50	52	Infect	N/A	Rad	None	N/A
		U/Rabbit	0	Wound	0	32	67	Infect	N/A		None	N/A
		U/Rabbit	0	Wound	0	12	58	Infect	N/A		Bio(I)	None
		U/Rabbit	0	Wound	0	13	8	Infect	N/A		S(IM+I)	44
		U/Rabbit	0	Wound	0	12	50	Infect	N/A		P(I)	None
		U/Rabbit	0	Wound	0	12	8	Infect	N/A		P(IM)	44
		U/Rabbit	600	Wound	0	42	88	Infect	N/A	Syner	None	N/A
		U/Rabbit	600	Wound	0	50	100	Infect	N/A	Syner	Bio(I)	None
		U/Rabbit	600	Wound	0	16	31	Infect	N/A	Rad	Bio(L)	57
		U/Rabbit	600	Wound	0	30	80	Infect	N/A		S(L)	None
		U/Rabbit	600	Wound	0	21	33	Infect	N/A	Rad	S(IM)	55
		U/Rabbit	600	Wound	0	35	34	Infect	N/A	Rad	S(IM+L)	54
		U/Rabbit	600	Wound	0	31	39	Infect	N/A	Rad	S(IM+I)	49
		U/Rabbit	600	Wound	0	37	67	Infect	N/A	Rad	P(Inj)L	21
		U/Rabbit	600	Wound	0	58	23	Infect	N/A	Rad	P(IM)	65
		U/Rabbit	600	Wound	0	122	30	Infect	N/A	Rad	P(L+IM)	58
		U/Rabbit	600	Wound	0	50	40	Infect	N/A	Rad	P+S	47
		U/Rabbit	0	Wound	N/A	4	25	Infect	N/A		None	N/A
		U/Rabbit	0	Wound	N/A	6	17	Infect	N/A		Bic(IM)	8
		U/Rabbit	600	Wound	0	11	64	Infect	N/A	Syner	None	N/A
		U/Rabbit	600	Wound	0	27	37	Infect	N/A	Rad	Bic(IM)	27

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